1. MEDICATIONS

Several clinical questions were considered by the National Asthma Education and Prevention Program (NAEPP) Expert Panel regarding medications used in asthma therapy, including questions about the effectiveness of inhaled corticosteroids compared to other long-term-control medications in the management of asthma in children, the safety of long-term use of inhaled corticosteroids in children, the use of combination therapy in treating moderate persistent asthma, and the use of antibiotics in treating acute exacerbations of asthma. This section on medications will present each clinical question separately, and each discussion will include a statement of the specific question; a summary answer to the question; the rationale for the question; a summary of the systematic review of the evidence (SRE), as well as additional literature considered by the Expert Panel after the systematic review was completed; recommendations for updating the *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma;* and recommendations for future research.

LONG-TERM MANAGEMENT OF ASTHMA IN CHILDREN: EFFECTIVENESS OF INHALED CORTICOSTEROIDS COMPARED TO OTHER MEDICATIONS

Question

Does chronic use of inhaled corticosteroids improve long-term outcomes for children with mild or moderate persistent asthma, in comparison to the following treatments?

- ***"As-needed" beta$_2$-agonists?***
- ***Long-acting beta$_2$-agonists?***
- ***Theophylline?***
- ***Cromolyn/nedocromil?***
- ***Combinations of above drugs?***

Leukotriene modifiers (leukotriene receptor antagonists [LTRAs] and 5-lipoxygenase inhibitors) were not included in the SRE because no published data meeting minimal inclusion criteria for children were available to compare this class of compounds directly to any other long-term-control medications, including inhaled corticosteroids. Studies on LTRAs in children that were published subsequent to the SRE were considered by the Expert Panel as additional information and included in the comprehensive review of the question.

Summary Answer to the Question

Strong evidence establishes that inhaled corticosteroids improve long-term outcomes for children of all ages with mild or moderate persistent asthma, compared to as-needed beta$_2$-agonists, as measured by prebronchodilator forced expiratory volume in 1 second (FEV$_1$), reduced hyperresponsiveness, improvements in symptom scores, fewer courses of oral corticosteroids, and fewer urgent care visits or hospitalizations (SRE-Evidence A). Studies comparing inhaled corticosteroids to cromolyn, nedocromil, theophylline, or LTRAs are limited, but available evidence shows that none of these long-term-control medications is as effective as inhaled corticosteroids in improving asthma outcomes (SRE-Evidence B; Evidence B, C). (See Appendix A, Stepwise Approach for Managing Asthma, for the definition of asthma severity classifications.) A revision to the *NAEPP Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* (EPR-2) stepwise approach to therapy is recommended. The Expert Panel recommends the following therapy for children with mild persistent asthma:

- For children 5 years of age and older, the preferred therapy is inhaled corticosteroids (low dose) (SRE-Evidence A). Alternative therapies (listed alphabetically because there are insufficient data to enable ranking) include cromolyn, LTRAs, nedocromil, or sustained-release theophylline (SRE-Evidence A, B; Evidence A, B).
- For children younger than 5 years of age, no studies compare inhaled corticosteroids to other long-term-control medications. Therefore, recommendations are based on extrapolations of studies in older children. The preferred therapy is low-dose inhaled corticosteroids, with nebulizer, dry powder inhaler (DPI), or metered-dose inhaler (MDI) with holding chamber, with or without a face mask. Alternative therapies (listed alphabetically) include cromolyn or LTRA (SRE-Evidence B).

Rationale for the Question

The NAEPP recognizes the need for continual appraisal of the benefits and potential risks of asthma medications in children. The EPR-2 recommends inhaled corticosteroids, cromolyn, and nedocromil as preferred treatment, with acknowledgement of a potential but small risk of adverse events with the use of inhaled corticosteroids. The NAEPP considers it important to update information regarding the effectiveness and safety of inhaled cortico-steroids in children. A review of evidence on the safety of inhaled corticosteroids is presented later. To enrich the evaluation of effectiveness, the SRE searched the literature for studies comparing the effectiveness of inhaled corticosteroids used as monotherapy to short-acting beta$_2$-agonists taken as needed, and to other long-term-control medications used as monotherapy in children with mild or moderate persistent asthma. Such a review enables the NAEPP to consider the most appropriate position of various medications in the stepwise approach to asthma management, based on the current evidence. At the time that the EPR-2 was published, the following long-term-control medications were available for treatment in children: inhaled corticosteroids, long-acting inhaled beta$_2$-agonists (salmeterol), theophylline, cromolyn, nedocromil, and leukotriene modifiers (zafirlukast and zileuton); not all were approved for use in children younger than 5 years of age. Since the publication of the EPR-2, a third leukotriene modifier, montelukast, has become available for children 2 years of age and older, and a nebulized form of inhaled corticosteroids has become available for children as young as 1 year of age. The DPI forms of salmeterol and fluticasone, available for older children, also were approved down to 4 years of age.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

This question addresses long-term outcomes of treatment for children with mild or moderate persistent asthma. Outcomes of primary interest are those that indicate the progression of underlying disease; short-term measures of symptom control cannot adequately address this question. Of the available measures, longitudinal determination of postbronchodilator FEV_1 provides the best available measure of lung growth (CAMP Research Group 2000). Epidemiologic studies often use prebronchodilator FEV_1, which has been one of the strongest correlates with long-term outcomes. Peak expiratory flow (PEF) also can indicate long-term progression; both prebronchodilator FEV_1 and PEF are more subject to short-term changes in control and, of the two, PEF is the more variable measure. Other outcome measures, such as symptoms, medication use, and utilization measures, also are likely to correlate with long-term progression of disease over time, but are highly subject to changes in short-term control of bronchospasm.

In addition to the eligibility criteria for selecting studies related to all topics in the SRE (described in the Introduction), the following criteria were used to select studies for this question:

- Study design is a comparative or crossover clinical efficacy trial, with a concurrent control group.
- Study compares the use of inhaled corticosteroids vs. placebo; OR compares inhaled corticosteroids vs. no treatment control; OR compares inhaled corticosteroids vs. alternative medication for mild asthma (as-needed $beta_2$-agonists, theophylline, cromolyn, nedocromil, or combinations of these medications); OR compares *the addition of* inhaled corticosteroids to other medication for mild asthma (as-needed $beta_2$-agonists, theophylline, cromolyn, nedocromil, or combinations of these medications).
- Includes at least 10 evaluable, similarly treated patients per study arm or crossover phase with mild or moderate persistent asthma, with the following defined limits:
  - FEV_1 more than 60 percent of predicted; PEF variability more than 20 percent

OR
  - Symptoms more than 2 times a week to daily

OR
  - Nocturnal symptoms more than 2 times a month

OR
  - Population cannot be classified into the above categories but appears to include primarily persons with mild or moderate persistent asthma

OR
  - Population is mixed, but the majority appears to consist of persons with mild or moderate persistent asthma.
- Study duration is of at least 12 weeks.
- At least 90 percent of included patients have not been treated with other long-term-control medications (LTRAs, long-acting inhaled $beta_2$-agonists, inhaled corticosteroids) for at least 4 weeks before beginning to take inhaled corticosteroids.
- Enrolls only patients younger than 18 years of age or stratifies outcomes for patients younger than 18 years of age.
- Study addresses relevant outcomes.

Summary of Findings

Studies

Ten studies enrolling 2,210 patients met the inclusion criteria for this question. Three of the studies were based in the Netherlands (Hoekstra et al. 1996; Van Essen-Zandvliet et al. 1992; Verberne et al. 1997); two were from Scandinavia (Jonasson et al. 1998; Agertoft and Pedersen 1994); two from the United Kingdom (Storr et al. 1986; Connett et al. 1993); two from the United States (CAMP 2000; Tinkelman 1993); and one from Canada (Simons 1997). Nine of the 10 studies were randomized, double-blind, parallel-group trials. The most robust of these, the Childhood Asthma Management Program (CAMP) Research Group (CAMP 2000), is a three-arm trial enrolling 1,041 patients followed for 4 to 6 years that compared inhaled corticosteroids to nedocromil and with placebo. At present, the CAMP trial is the "largest, longest, and most comprehensive multicenter treatment trial for asthma ever attempted in the United States"(CAMP 2000). The remaining eight randomized trials are considerably smaller in size (range: 14 to 102 patients per study arm) and duration of followup (range: 1 to 2 years). The tenth trial (Agertoft and Pedersen 1994) was not randomized. (See the key evidence tables in this section for a summary description of the 10 studies that met the eligibility criteria for evaluation.) Publications comparing the use of LTRA in children to other long-term-control medications were not available at the time of the SRE.

Results of Studies

Inhaled Corticosteroids Compared to As-Needed $Beta_2$-Agonists

Children 5 Years of Age or Older

The evidence of the efficacy of inhaled corticosteroids in children older than 5 years of age was obtained from six trials, five of which were placebo controlled and randomized. These six trials enrolled a total of 790 patients treated with inhaled corticosteroids and 652 controls. The most robust evidence is from the CAMP trial, which contributed 40 percent (311) of the total inhaled corticosteroid patients and

64 percent (418) of the total controls, documented the longest duration of treatment (4 years), used the most complete outcome measures, and reported in the greatest detail the study design and statistical analysis.

Overall, these studies demonstrate that inhaled corticosteroids improve asthma control compared to as-needed beta$_2$-agonists without any other long-term-control medication. Inhaled corticosteroid-treated patients with mild or moderate persistent asthma demonstrate improvements in prebronchodilator FEV_1, reduced airway hyperresponsiveness, symptom scores and symptom frequency, less supplemental beta$_2$-agonist use, fewer courses of oral corticosteroids, and lower hospitalization utilization. The evidence does not suggest, however, that inhaled corticosteroid use is associated with improved long-term postbronchodilator FEV_1 which is a surrogate measure of lung growth. The CAMP trial reported no difference in the change in postbronchodilator FEV_1 after 4 years of treatment (CAMP 2000). No study reported any statistically significant result that favored the as-needed beta$_2$-agonist control group.

Children 5 Years of Age or Younger

Two small trials (69 participants, combined) compared inhaled corticosteroid treatment to placebo in children younger than 5 years of age. The available evidence is scant, but the results reported appear to be consistent with those reported for children older than 5 years of age: that inhaled corticosteroids improve short-term control of asthma. No studies that examine the long-term impact of inhaled corticosteroids on lung function in this age group are available.

Inhaled Corticosteroids Compared to Alternative Long-Term-Control Medications

No comparison studies are available for children younger than 5 years of age.

Long-Acting Inhaled Beta$_2$-Agonist (Salmeterol)

The available evidence is inadequate to make definitive conclusions about relative effectiveness of inhaled corticosteroids and salmeterol in children with mild or moderate persistent asthma. Two randomized and double-blinded trials enrolled 116 (99 evaluable) children treated with inhaled corticosteroids, 112 (83 evaluable) children treated with salmeterol, and 80 (55 evaluable) children treated with placebo. One of these is a three-arm trial in which most comparisons were indirect and reported as inhaled corticosteroids vs. placebo and salmeterol vs. placebo. Of the statistically significant results reported, most were significant in only one of the two trials; however, all results clearly favored inhaled corticosteroids over salmeterol as monotherapy. In one of the trials, measurements of FEV_1 deteriorated over time in those children receiving monotherapy with salmeterol (Verberne et al. 1997).

Theophylline

One trial compared the effectiveness of 1 year of treatment with theophylline or low-dose inhaled corticosteroids in 747 patients, 185 of whom were children (Reed 1998). Although conclusions are limited because of the large numbers of withdrawals and the absence of additional trials, the data from this study support the superior effectiveness for low-dose inhaled corticosteroids compared to theophylline. The inhaled corticosteroids were significantly more effective in reducing symptoms, supplemental bronchodilators and systemic corticosteroid doses, bronchial hyperresponsiveness, and eosinophilia. No outcomes were significantly superior with theophylline, which caused more headaches, nervousness, insomnia, and gastrointestinal distress; and more patients discontinued treatment because of side effects that occurred while they were taking theophylline.

Nedocromil

The CAMP trial found no differences between nedocromil and placebo in lung function or symptom outcomes, although courses of oral corticosteroids and urgent care visits were reduced (CAMP 2000). The primary analysis in this study compares two medications—nedocromil and inhaled corticosteroids—to placebo, rather than to each other. However, the magnitude of the effect of inhaled corticosteroids on all clinical outcomes, along with the marginal effect of nedocromil on just two, supports the conclusion that inhaled corticosteroids are more effective than nedocromil in reducing the frequency and severity of symptoms, supplemental beta$_2$-agonist use, and the frequency of hospitalizations due to asthma.

Additional Literature/Information

Additional data were reviewed to include information that was published since the SRE was performed and to consider leukotriene modifiers.

Inhaled Corticosteroids

A recent study confirmed the effectiveness of inhaled corticosteroids in improving symptoms, airway hyperresponsiveness, and lung function in children 2 to 5 years of age (Nielsen and Bisgaard 2000).

Cromolyn and Nedocromil

A consideration of the precise relationship of cromolyn and nedocromil among other long-term-control medications in the treatment of persistent asthma continues to be difficult based on the few available comparison studies. These two medications have distinct properties but similar mechanisms of action. They have been shown to provide symptom control greater than placebo in some clinical trials (Konig 1997; Petty et al. 1989) and to confer protection against exacerbations of asthma leading to hospitalization, particularly in children (Donahue et al. 1997) and emergency department visits (Adams et al. 2001). These results, along with the excellent safety profile, justify consideration of these medications as treatment options. However, when data regarding the efficacy of cromolyn recently were systematically reviewed (Taschle et al. 2000), the authors concluded that insufficient evidence existed to conclude that cromolyn had a beneficial effect on maintenance treatment of childhood asthma. Compared to placebo, nedocromil reduces urgent care visits as well as the need for prednisone, which are meaningful clinical outcomes. However, nedocromil is no different than placebo on all other outcome measures (CAMP 2000). Overall, nedocromil is significantly less effective in improving outcome measures than inhaled corticosteroids (CAMP 2000). Nedocromil has not been adequately studied in children younger than 5 years of age.

As a result of these disparate findings on cromolyn and nedocromil (i.e., some, but limited effectiveness and strong safety profile), the Expert Panel's opinion is that cromolyn for children of all ages and nedocromil for children older than 5 years of age could be considered in the treatment of persistent asthma, but they are not preferred therapies (SRE-Evidence A; Evidence B, C).

Leukotriene Modifiers

Leukotriene modifiers comprise two pharmacologic classes of compounds: 5-lipoxygenase pathway inhibitors (e.g., zileuton), and LTRAs (e.g., zafirlukast and montelukast). Only zafirlukast (for children as young as 7 years of age) (Pearlman et al. 2000; Weinberger 2000) and montelukast (for children as young as 2 years of age) (Knorr et al. 1998; Knorr et al. 2001) are approved for use in children. Zileuton has been demonstrated to control asthma more effectively than placebo (Israel et al. 1996) and comparably to theophylline (Schwartz et al. 1998) in adult patients with persistent symptoms; studies in children have not been reported yet.

The LTRAs have been demonstrated to provide statistically significant but modest improvement in lung function when used as monotherapy in both adults and children as young as 6 years of age and in asthma control outcomes other than lung function in patients as young as 2 years of age (Pearlman et al. 2000; Knorr et al. 1998; Knorr et al. 2001; Israel et al. 1996; Schwartz et al. 1998; Altman et al. 1998; Busse et al. 2001; Kemp et al. 1998; Nathan et al. 1998; Tashkin et al. 1999; Bleecker et al. 2000; DuBuske et al. 1997). In general, these studies included patients with either mild or moderate persistent asthma, although the classification of severity was not always clear in the studies, nor consistently applied. When comparing overall efficacy of LTRAs to inhaled corticosteroids in adult patients with persistent asthma, most outcome measures significantly and clearly favored inhaled corticosteroids (Busse et al. 2001). Therefore, based on the available data comparing LTRAs to inhaled corticosteroids, the Expert Panel concludes that inhaled corticosteroids should be the preferred treatment option for mild persistent asthma in adults and, by extrapolation until published comparison data become available, for children (Evidence B, C). (See Medications: Combination Therapy for recommendations on the use of LTRAs in moderate asthma.) Due to the lack of randomized controlled trials (RCTs) in children less than 12 years of age, zileuton cannot be recommended for use in children.

Long-Acting Inhaled Beta$_2$-Agonists

In a recent study, 164 patients ages 12 through 65 years whose asthma was well controlled on 400 mcg twice daily of inhaled corticosteroids were randomly assigned to continue inhaled corticosteroids or switch to long-acting inhaled beta$_2$-agonists, 42 mcg twice daily. During the 16-week study, clinical outcomes did not differ significantly. However, those on long-acting inhaled beta$_2$-agonists experienced significantly more treatment failures (24 percent vs. 6 percent) and asthma exacerbations (20 percent vs. 7 percent) than those remaining on inhaled corticosteroids (Lazarus et al. 2001). These results, favoring use of inhaled corticosteroids over long-acting beta$_2$-agonists as monotherapy, support the findings of the studies in children that were noted in the SRE.

Recommendations for EPR Update

The Expert Panel recommends revising EPR-2, based on review of the SRE and additional data and clinical experience. The following key changes are described:

- Based on the SRE, inhaled corticosteroids are the preferred treatment for initiating therapy in children of all ages with persistent asthma (SRE-Evidence A, B). Thus, the Expert Panel no longer recommends consideration of an initial therapeutic trial with cromolyn or nedocromil. Current scientific evidence demonstrates the superiority of inhaled corticosteroids.
- LTRAs are available for children as young as 2 years of age, and studies have demonstrated improved outcomes (Evidence B). LTRAs are an alternative—although not preferred—treatment (Evidence B) and are considered if patient circumstances regarding administration of inhaled corticosteroids warrants selection of oral treatment (Evidence D).
- Based on epidemiologic study of wheezing in early childhood, it is the opinion of the Expert Panel that the initiation of long-term-control therapy should be considered strongly for infants and young children who in the past year have had more than three episodes of wheezing that lasted more than 1 day and affected sleep, and who in addition have identifiable risk factors for the development of asthma (Evidence D). This is in addition to previously recommended indications for initiating long-term-control therapy (i.e., children requiring symptomatic treatment more than 2 times a week or experiencing severe exacerbations less than 6 weeks apart).

Specifically, the Expert Panel recommends that the text of EPR-2 be revised to read as follows in the EPR-2 sections: The Medications and the Stepwise Approach for Managing Asthma; **the shaded text indicates new text.**

Recommended changes to The Medications (pages 59 through 67 in EPR-2)

Key Points: The Medications (page 59 in EPR-2):

- **Cromolyn and nedocromil:** Used as alternative, but not preferred, medications for the treatment of mild persistent asthma (Evidence A, B). Can also be used as preventive treatment prior to exercise or unavoidable exposure to known allergens.

- **Long-acting inhaled beta$_2$-agonists:** Long-acting bronchodilator used concomitantly with inhaled corticosteroids is the preferred combination therapy for long-term control and prevention of symptoms in moderate and severe persistent asthma (Evidence A, B). Also prevents exercise-induced bronchospasm (EIB).
- **Leukotriene modifiers:** The leukotriene receptor antagonists (LTRAs) montelukast (for patients ≥2 years of age) and zafirlukast (for patients ≥ 7 years of age), or the 5-lipoxygenase inhibitor zileuton (for patients ≥12 years of age), are alternative, but not preferred, therapies for the treatment of mild persistent asthma (Evidence B). Leukotriene modifiers also may be used with inhaled corticosteroids as combination therapy in the treatment of moderate persistent asthma (Evidence B).

Corticosteroids (page 60 in EPR-2)

Insert after the third sentence.

The evidence of the efficacy of inhaled corticsteroids in children older than 5 years of age was obtained from six trials, five of which were placebo controlled and randomized (see NAEPP Expert Panel Report Update-2000 for complete references). Overall, these studies demonstrate that inhaled corticosteroids improve asthma control compared to as-needed beta$_2$-agonists without any other long-term-control medication (Evidence A). Inhaled corticosteroid-treated patients with mild or moderate persistent asthma demonstrate improvements in prebronchodilator FEV_1, reduced airway hyperresponsiveness, symptom scores and symptom frequency, less supplemental beta$_2$-agonist use, fewer courses of oral corticosteroids, and lower hospitalization utilization. The evidence does not suggest, however, that inhaled corticosteroid use is associated with improved long-term postbronchodilator FEV_1, which is a surrogate measure of lung growth. No study reported any statistically significant result that favored the as-needed beta$_2$-agonist control group. Studies comparing inhaled corticosteroids to cromolyn, nedocromil, theophylline, or LTRAs are limited, but available evidence shows that none of these long-term-control medications appear to be as effective as inhaled corticosteroids in improving asthma outcomes (Evidence A, B).

Cromolyn Sodium and Nedocromil (page 60 in EPR-2)

Replace the third paragraph of text with the following.

Cromolyn sodium and nedocromil have been shown to provide symptom control greater than placebo in some clinical trials (Konig 1997; Petty et al. 1989) and to confer protection against exacerbations of asthma leading to hospitalization, particularly in children (Donahue et al. 1997) and emergency department visits (Adams et al. 2001) These results, along with the excellent safety profile, justify consideration of these medications as treatment options. However, when data regarding the efficacy of cromolyn recently were systematically reviewed (Taschle et al. 2000), the authors concluded that insufficient evidence existed to conclude that cromolyn had a beneficial effect on maintenance treatment of childhood asthma. Compared to placebo, nedocromil reduces urgent care visits as well as the need for prednisone, which are meaningful clinical outcomes. However, nedocromil is no different than placebo on all other outcome measures (CAMP 2000). Overall, nedocromil is significantly less effective in improving outcomes measures than inhaled corticosteroids (CAMP 2000). Nedocromil has not been adequately studied in children younger than 5 years of age. As a result of these disparate findings on cromolyn and nedocromil (i.e., some, but limited effectiveness and strong safety profile), the Expert Panel's opinion is that cromolyn for children of all ages and nedocromil for children older than 5 years of age could be considered in the treatment of persistent asthma, but they are not preferred therapies (Evidence A, B, C).

Leukotriene Modifiers (page 65 in EPR-2)

Replace the second paragraph of text with the following.

Three leukotriene modifiers—montelukast, zafirlukast and zileuton—are available as oral tablets for the treatment of asthma. Leukotriene modifiers comprise two pharmacologic classes of compounds: 5-lipooxygenase pathway inhibitors (e.g., zileuton), and LTRAs (e.g., montelukast and zafirlukast). Only zafirlukast (for children as young as 7 years of age) and montelukast (for children as young as 2 years of age) are approved for use in children. Zileuton has been demonstrated to control asthma more effectively than placebo (Israel et al. 1996) and comparably to theophylline (Schwartz et al. 1998) in adult patients with persistent symptoms; studies in children have not been reported yet.

The LTRAs have been demonstrated to provide statistically significant but modest improvement in lung function when used as monotherapy in both adults and children as young as 6 years of age and in asthma control outcomes other than lung function in patients as young as 2 years of age (Pearlman et al. 2000; Knorr et al. 1998; Knorr et al. 2001; Israel et al. 1996; Schwartz et al. 1998; Altman et al. 1998; Busse et al. 2001; Kemp et al. 1998; Nathan et al. 1998; Tashkin et al. 1999; Bleecker et al. 2000; DuBuske et al. 1997). In general, these studies included patients with either mild or moderate persistent asthma, although the classification of severity was not always clear in the studies, nor consistently applied. When comparing overall efficacy of LTRAs to inhaled corticosteroids in adult patients with persistent asthma, most outcome measures significantly and clearly favored inhaled corticosteroids (Busse et al. 2001).

Insert as the final paragraph.

Therefore, based on the available data comparing LTRAs to inhaled corticosteroids, the Expert Panel concludes that inhaled corticosteroids should be the preferred treatment option for mild persistent asthma in adults, and by extrapolation until published comparison data become available, for children (Evidence B, C). Five published studies evaluated the addition of leukotriene modifiers to fixed doses of inhaled corticosteroids; none compared the combination to increasing the dose of inhaled corticosteroids. Limitations of these studies preclude definitive conclusions, but they reveal a trend showing improvement in lung function and, in some, symptoms from the combination of leukotriene modifiers and inhaled corticosteroids compared with a fixed dose of inhaled corticosteroids alone.

Figure 3–1. Long-Term-Control Medications (page 63 in EPR-2)

Long-Acting Inhaled Beta$_2$-Agonists. Add in "Therapeutic Issues" column: Treatment of choice in combination with inhaled corticosteroids for treatment of moderate persistent asthma in adults and children over 5 years of age.

Leukotriene Modifiers. Add: Montelukast tablets: long-term control and prevention of symptoms in mild persistent asthma for patients ≥2 years of age. May also be used with inhaled corticosteroids as combination therapy in moderate persistent asthma. Zafirlukast: Change age zafirlukast to ≥7 years of age. And Add: May also be used with inhaled corticosteroids as combination therapy in moderate persistent asthma. Zileuton: add: May also be used with inhaled corticosteroids as combination therapy in moderate persistent asthma.

Figure 3–2. Quick-Relief Medications (page 64 in EPR-2)

Short-Acting Inhaled Beta$_2$-Agonists. Add: Levalbuterol

Recommended changes to The Stepwise Approach to Managing Asthma; mild persistent asthma (step 2 care) (pages 85 through 97 in EPR-2).

Revisions of EPR-2 on moderate persistent asthma (step 3 care) are presented in the section "Medications: Combination Therapy."

Figure 3–4b. Stepwise Approach for Managing Asthma in Adults and Children Older than 5 Years of Age: Treatment (page 85 in EPR-2)

Step 2

Mild Persistent

One daily long-term-control medication

Preferred treatment:

Inhaled corticosteroids (low dose)

Alternative treatment (listed alphabetically):

Cromolyn

OR

Leukotriene modifier (only LTRAs are recommended for use in children)

OR

Nedocromil

OR

Sustained release theophylline to serum concentrations of 5–15 µg/mL.

Step 3 and Step 4

Please refer to the Medications: Combination Therapy.

Key Recommendations box for managing asthma in school-age children and adolescents (page 97 in EPR-2)

- Pulmonary function testing should use appropriate reference populations. Adolescents compare better to childhood than to adult predicted norms.
- When initiating daily long-term-control therapy for mild or moderate persistent asthma, the choice of medication includes consideration of treatment effectiveness, the individual patient's history of previous response to therapies, the ability of the patient and family to correctly use the medication, and anticipated patient and family adherence with the treatment regime (Evidence D).
- Adolescents (and younger children when appropriate) should be directly involved in establishing goals for therapy and developing their asthma management plans.
- Active participation in physical activities, exercise, and sports should be promoted.
- A written asthma management plan should be prepared for the student's school and should include plans to ensure reliable, prompt access to medications. Either encourage parents to take a copy to the child's school or obtain parental permission and send a copy to the school nurse or designee (Evidence D).

Figure 3–6. Stepwise Approach for Managing Infants and Young Children (5 Years of Age and Younger) With Acute or Chronic Asthma Symptoms (page 96 in EPR-2)

Step 2

Mild Persistent

One daily long-term-control medication

Preferred treatment:

Low-dose inhaled corticosteroids (with nebulizer OR MDI with holding chamber with or without a face mask OR DPI)

Alternative treatment (listed in alphabetical order):

Cromolyn (nebulizer is preferred; or MDI with holding chamber)

OR

Leukotriene receptor antagonist

Step 3

Moderate Persistent

Preferred treatment:

Low-dose inhaled corticosteroids and long-acting beta$_2$-agonists

OR

Medium-dose inhaled corticosteroids

Alternative treatment:

Low-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline.

If needed (particularly in patients with recurring severe exacerbations):

Preferred treatment: Medium-dose inhaled corticosteroids and long-acting beta$_2$-agonists.

Alternative treatment: Medium-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline.

Special considerations for managing asthma in different groups: infants and young children (5 years of age and younger), key recommendations (pages 94 through 97 in EPR-2)

- Diagnosing asthma in infants is often difficult, yet underdiagnosis and undertreatment are key problems in this age group. Thus, a diagnostic trial of inhaled bronchodilators and anti-inflammatory medications may be helpful.
- Treatment for infants and young children with asthma has not been adequately studied. Recommendations for treatment are based on extrapolations from studies in older children and adults.
- The initiation of long-term-control therapy should be strongly considered in the following circumstances, in the opinion of the Expert Panel (Evidence D):
  - Infants and young children who had more than three episodes of wheezing in the past year that lasted more than 1 day and affected sleep AND who have a high risk of developing persistent asthma as indicated by either (a) a physician diagnosis of atopic dermatitis or a parental history of asthma OR (b) two of the following conditions: physician-diagnosed allergic rhinitis, greater than 4 percent peripheral blood eosinophilia, or wheezing apart from colds (Martinez et al. 1995; Martinez 1995; Castro-Rodriguez 2000).
  - Infants and young children consistently requiring symptomatic treatment more than 2 times per week should be given daily long-term-control therapy.
  - Infants and young children who have severe exacerbations (requiring inhaled beta$_2$-agonist more frequently than every 4 hours over 24 hours) that occur less than 6 weeks apart.
  - When initiating daily long-term-control therapy, inhaled corticosteroids are the preferred treatment (SRE-Evidence B). Alternative treatment options (listed here in alphabetical order because there are insufficient data to enable ranking) include cromolyn and LTRA (montelukast) (Evidence B). The initial choice of long-term-control medication includes consideration of treatment effectiveness, the individual patient's history of previous response to therapies, the ability of the patient and family to correctly use the medication, and anticipated patient and family adherence to the treatment regimen (Evidence D).
  - Response to therapy should be carefully monitored. Once control of asthma symptoms is established and sustained, a careful step down in therapy should be attempted. If clear benefit is not observed within 4 to 6 weeks, alternative therapies or diagnoses should be considered (Evidence D).

Diagnosis

Several studies show that as many as 50 to 80 percent of children with asthma develop symptoms before their fifth birthdays. Diagnosis can be difficult in this age group and has important implications. On the one hand, asthma in early childhood is frequently underdiagnosed (receiving such labels as chronic bronchitis, wheezy bronchitis, recurrent pneumonia, gastroesophageal reflux, and recurrent upper respiratory tract infections), and thus many infants and young children do not receive adequate therapy. On the other hand, not all wheezes and coughs are caused by asthma, and caution is needed to avoid giving infants and young children inappropriately prolonged asthma therapy. Episodic or chronic wheezing, coughing, and breathlessness also may be seen in other less common conditions, including cystic fibrosis, vascular ring, tracheomalacia, primary immunodeficiency, congenital heart disease, parasitic disease, and foreign body aspiration.

Among children 5 years of age and younger, the most common cause of asthma-like symptoms is viral respiratory infection. At present, the relative contributions of airway inflammation, bronchial smooth-muscle abnormalities, or other structural factors in producing wheeze with acute viral upper respiratory infections are unknown. There appear to be two general patterns of illness in infants and children who wheeze with acute viral upper respiratory infections: a remission of symptoms in the preschool years and persistence of asthma throughout childhood. No clear markers are available to predict the prognosis of an individual child; however, in infants and young children under 5 years of age with frequent wheezing (for example, more than three episodes in the past year that lasted more than 1 day and affected sleep), risk factors significantly associated with persistent asthma at 6 years of age include having either (a) parental asthma history or a physician diagnosis of atopic dermatitis or (b) two of the following conditions: physician-diagnosed allergic rhinitis, peripheral blood eosinophilia, or wheezing apart from cold (Evidence C) (Castro-Rodriguez et al. 2000; Martinez 1995). Although currently not established, it is conceivable that early recognition and treatment of these high-risk children could result in secondary prevention of childhood asthma.

Diagnosis is complicated by the difficulty in obtaining objective measurements of lung function in this age group. Essential elements in the evaluation include the history, symptoms, physical examination, and assessment of quality of life. A therapeutic trial with medications listed in figure 3–5d also will aid in the diagnosis.

Treatment

Figure 3–6 illustrates the Expert Panel's recommendations for a stepwise approach to managing acute and chronic asthma symptoms, regardless of the prognosis for the wheezing infant or young child.

It is the opinion of the Expert Panel that, in general, daily long-term-control therapy should be initiated

in infants and young children consistently requiring symptomatic treatment more than 2 times per week and in infants and young children who experience severe exacerbations (requiring inhaled beta$_2$-agonist more frequently than every 4 hours over 24 hours) that occur less than 6 weeks apart. It is the opinion of the Expert Panel that the initiation of long-term-control therapy should also be strongly considered in infants and young children who had more than three episodes of wheezing in the past year that lasted more than 1 day and affected sleep AND who have risk factors for developing persistent asthma: either (a) parental history of asthma or a physician diagnosis of atopic dermatitis or (b) two of the following conditions: physician-diagnosed allergic rhinitis, greater than 4 percent peripheral blood eosinophilia, or wheezing apart from colds (Evidence D).

The following have been Food and Drug Administration (FDA)-approved for young children: the inhaled corticosteroids budesonide nebulizer solution (approved for children 1 to 8 years of age) and fluticasone DPI (approved for children 4 years of age and older); the long-acting beta$_2$-agonist salmeterol DPI (approved for children 4 years of age and older); and, based on safety data rather than efficacy data, the LTRA montelukast 4 mg chewable tablet (approved for children 2 to 6 years of age).

At present, there are few studies of medications in children younger than 3 years of age. A therapeutic trial of anti-inflammatory medications should be monitored carefully. Treatment should be stopped if a clear beneficial effect is not obvious within 4 to 6 weeks. Inhaled corticosteroids have been shown to be effective in long-term clinical studies with infants; in contrast, cromolyn has inconsistently demonstrated symptom control in children younger than 5 years of age (Tasche et al. 2000). A LTRA (montelukast) 4 mg chewable tablet has shown some effectiveness in children 2 to 5 years of age (Knorr et al. 2001). Sustained-release theophylline is not recommended as an alternative long-term-control medication for young children with mild persistent asthma because it may have particular risks of adverse side effects in infants who frequently have febrile illnesses, which increase theophylline concentrations. Theophylline may be considered as adjunctive therapy in young children with moderate or severe persistent asthma if there are cost considerations, but only if serum concentration levels will be carefully monitored.

In deciding when to initiate daily long-term-control therapy, the clinician must weigh the possible long-term effects of inadequately controlled asthma vs. the possible adverse effects of medications given over prolonged periods. There is evidence that anti-inflammatory treatment can reduce morbidity from wheezing in early childhood (Connett et al. 1993). Long-term studies in children 5 to 12 years of age at the time of enrollment conclude that inhaled corticosteroids improve health outcomes for children with mild or moderate persistent asthma and that the potential albeit small risk of delayed growth from the use of inhaled corticosteroids is well balanced by their effectiveness (CAMP 2000). Further, available long-term data indicate that most children treated with recommended doses of inhaled corticosteroids achieve their predicted adult heights (Agertoft and Pedersen 2000). It is noted that the long-term prospective studies on growth involved budesonide, and that the retrospective analyses included studies on beclomethasone, but the results have been generalized to include all inhaled corticosteroid preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies on numerous preparations suggest that the effect of inhaled corticosteroids on growth is a drug class effect. In children with demonstrable adverse effects related to inhaled corticosteroid therapy, other options (cromolyn, LTRA, nedocromil, or theophylline) for initiating and maintaining long-term-control therapy are available. **Thus, based on high-quality evidence, the Expert Panel recommends long-term-control therapy for children with mild or moderate persistent asthma because it provides control and prevention of asthma symptoms (SRE-Evidence A). However, evidence to date is insufficient to permit conclusions regarding whether early vs. delayed intervention with daily long-term-control medication will alter the underlying course of the disease.** Although a preliminary study suggests that appropriate control of childhood asthma may prevent more serious asthma or irreversible obstruction in later years (Agertoft and Pedersen 1994), these observations were not verified in a recent long-term randomized controlled trial in children ages 5 to 12 years (CAMP 2000). The best available evidence does not support the assumption that children 5 to 12 years of age with mild or moderate persistent asthma have a progressive decline in lung function that can be prevented by early initiation of long-term-control medications. Observational prospective data from other large groups of children suggest that the timing of the CAMP intervention was too late, as most loss of lung function in early childhood asthma appears to occur during the first 3 to 5 years of life (Martinez et al. 1995). However, it has not yet been determined whether early recognition of children at high risk of developing persistent asthma coupled with early therapeutic intervention will either prevent the loss of lung function or prevent the development of persistent disease. Currently, critical prospective studies to address these issues are in progress.

Recommendations for treating infants and young children at different steps of care include:

- **The patient's response to therapy should be monitored carefully. When benefits are sustained for 2 to 4 months, a step down in therapy should be attempted. If there are no clear benefits within 4 to 6 weeks, treatment should be stopped and alternative therapies or diagnoses should be considered (Evidence D).**
- **For step 2 care (mild persistent asthma), daily long-term-control therapy with an inhaled corticosteroid is the preferred option; cromolyn and LTRA**

are alternative therapies, (SRE-Evidence A, B; Evidence B). A trial of LTRA in children 2 years of age or older can be considered in situations in which inhaled medication delivery is suboptimal due to poor technique or adherence (Evidence D).

- **When inhaled corticosteroids are introduced in step 2 care, doses should be in the low range. Inhaled corticosteroids are now available in both MDI and nebulizer preparations. (See figures 3–5b and 3–5c in EPR-2 for discussion of equivalency among preparations.)**
- For step 3 care (moderate persistent asthma), there are no data available that compare treatments in step 3 care for infants and young children who are not well controlled on low doses of inhaled corticosteroids. Recommendations are based on expert opinion and extrapolation from studies in older patients. (See Medications: Combination Therapy.) **There are two main choices for step 3 care therapy: adding long-acting inhaled beta$_2$-agonists to low-dose inhaled corticosteroids (SRE-Evidence B; extrapolation from studies in older children) OR increasing the dose of inhaled corticosteroids within the medium-dose range (Evidence D).** Alternative but not preferred options are adding either a LTRA or theophylline (if serum concentrations are monitored) to low-to-medium doses of inhaled corticosteroids (Evidence D).

Comparative studies in older children and adults consistently favor combination therapy over increasing doses of inhaled corticosteroids. Because studies indicate that the potential for side effects of inhaled corticosteroids, though small, appears to be dose related and has been demonstrated in this age group at the medium-dose range of inhaled corticosteroids (Bisgaard 2002), the approach of adding long-acting inhaled beta$_2$-agonists to a lower dose of inhaled corticosteroids is one preferred option (Evidence B-extrapolating from adult studies). On the other hand, there are no data on long-acting beta$_2$-agonists in children under 4 years of age, and studies in infants and young children have shown medium doses of inhaled corticosteroids to be effective in treating moderate and severe asthma (Connet 1993, de Blic 1996, Bisgaard 1999, Nielsen 2000). The few studies available in this age group that have directly compared different doses of inhaled corticosteroids have shown that increasing the dose is most effective in reducing asthma exacerbations (Bisgaard 1999) and less consistently effective in improving other outcomes (Bisgaard 1999, Baker 1999, Kemp 1999). These results also have been found in studies of adults. Therefore, it is the opinion of the Expert Panel that using medium doses of inhaled corticosteroids as monotherapy for moderate asthma is another preferred treatment option.

For all treatments, it is essential to monitor the child's response to therapy. If there is no clear response within 4 to 6 weeks, the therapy should be discontinued and alternative therapies or alternative diagnoses considered. If there is a clear and positive response after 2 to 4 months, a step down in therapy should be undertaken to the lowest possible doses of medication required to maintain asthma control (Baker 1999; Kemp, Skoner, Szefler et al. 1999).

- Exacerbations caused by viral respiratory infections may be intermittent yet severe. **Consider systemic corticosteroids if the exacerbation is moderate to severe or at the onset of a viral respiratory infection if the patient has a history of severe exacerbations.**
- **Consultation with an asthma specialist should be *considered* for infants and young children requiring step 2 care; consultation is *recommended* for those requiring step 3 or step 4 care.**
- Several delivery devices are available for infants and young children. The dose received may vary considerably among devices and age groups. (See figure 3–3 for a summary of therapeutic issues regarding aerosol delivery devices.) The child's caregivers must be instructed in the proper use of appropriately sized face masks, spacers/holding chambers with face masks, and spacers/holding chambers for medication delivery to be effective and efficient. For children 2 years of age and younger, nebulizer therapy with mask may be preferred for administering aerosol medications. Children between 3 and 5 years of age may begin therapy with MDI and spacer/holding chamber alone, but if the desired therapeutic effects are not achieved, they may require a nebulizer or an MDI plus spacer/holding chamber and face mask.

Recommendations for Future Research

- How do LTRAs and inhaled corticosteroids compare in safety and efficacy in both the short term and long term in the treatment of mild persistent asthma in children younger than 5 years of age?
- Do anticipated differences in adherence to medication regimens (for example, inhalation therapy vs. oral tablet dose therapy) translate into significant clinical differences in overall asthma control?
- What is the best form of adjunctive therapy in children with moderate persistent asthma who are not adequately controlled on inhaled corticosteroid therapy alone? Long acting beta$_2$-agonists? LTRAs? Theophylline?
- Can response to various long-term-control medications be predicted prior to initiating treatment? Phenotype and genotype characterizations and definitions are needed to address this question.
- What is the most effective way of treating children who have only viral-induced asthma symptoms?
- Is drug delivery using an MDI with spacer equal in efficacy to nebulizer treatments in childhood asthma?
- Can early recognition and treatment of an infant or young child at high risk of developing asthma prevent development of persistent asthma?

Key Evidence Tables

TABLE 1–1. Inhaled Corticosteroids vs. No Inhaled Corticosteroids

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD
Children older than 5 years				
Childhood Asthma Management Research Group 2000a	Placebo	418	411	9 +/- 2.2
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BUD	311	306	9 +/-2.1
Jonasson, Carlsen, Blomqvist et al. 1998	Placebo	40	40	9.6
Randomized, parallel-arm, double-blinded, placebo-controlled trial				
	BUD 1	40	40	10.2
	BUD 2	42	42	10.0
	BUD 3	41	41	9.8
Simons 1997	Placebo	55	52	9.5 +/-2.4
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BDP	81	67	9.6 +/-2.6
Hoekstra, Grol, Hovenga et al. 1998	Placebo	19	15	11 +/-1.8
Randomized, parallel-arm, double-blinded, placebo-controlled trial	FP	15	25	10.6 +/-1.8
Agertoft and Pedersen 1994	Placebo	62	NR	6.1
Parallel-arm-controlled trial				
	BUD	216	NR	6.2
van Essen-Zandvliet, Hughes, Waalkens, et al. 1992	Placebo	58	17	10.9 +/- 1.9
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BUD	58	29	11 +/- 1.9
Children younger than 5 years				
Storr, Lenney and Lenney 1986	Placebo	14	13	3.4 +/- 1.5
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BDP	15	15	3.6 +/- 1.2
Connett, Warde, Wooler et al. 1993	Placebo	20	19	1.9 +/- 0.5
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BUD	20	17	1.7 +/- 0.6

Key: BDP = beclomethasone dipropionate, BUD = budesonide, FEV = forced expiratory flow, FP = fluticasone propionate, NR = not reported
PEF = peak expiratory flow, SD = standard deviation, Sx = symptom, X = outcome report
Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001

Estimated Disease Severity	Study Duration (weeks)	Lung Function Outcomes: FEV$_1$	PEF	PC20	Sx/Meds	Utilization Outcomes	Comments
Mild or Moderate	224	X	X	X	X	X	
Mild or Moderate	224	X	X	X	X	X	
Mild	12	X	X	X	X		Not stated how patients with moderate-severe asthma were excluded
Mild	12	X	X	X	X		
Mild	12	X	X	X	X		
Mild	12	X	X	X	X		
Mild or Moderate	52	X	X	X	X	X	
Mild or Moderate	52	X	X	X	X	X	
Mild or Moderate	12	X	X	X			
Mild or Moderate	12	X	X	X			
Mild or Severe	270.4 (mean)	X				X	Control patients were those patients who declined recommendation to take inhaled corticosteroids. Inhaled corticosteroid-free period after diagnosis is referred to as the run-in period, equal to at least 1 year.
Mild or Severe	192.4 (mean)	X				X	
Mild or Severe	95.3 (median)	X	X	X		X	Pharmaceutical company supplied study medication.
Mild or Severe	95.3 (median)	X	X	X		X	
Unable to estimate	26				X		Study took place over an 18-month period in an attempt to eliminate seasonal bias.
Unable to estimate	26				X		
Unable to estimate	26				X	X	Patients treated for up to 6 months, included in analysis if treated at least 5 weeks.
Unable to estimate	26				X	X	Study medication adjusted to 200–400 mcg 2x/day budesonide or 1–2 puffs 2x/day placebo depending on clinical need.

TABLE 1–2a. Inhaled Corticosteroids vs. Long-Acting Inhaled Beta$_2$-Agonists

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD
Verberne, Frost, Roorda et al. 1997	Salmeterol	35	25	10.6 +/- 2.9
Randomized, parallel-arm, double-blinded controlled trial	BDP	35	32	10.5 +/- 2.3
Simons 1997				
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BDP	81	67	9.6 +/- 2.6
	Salmeterol	80	58	8.8 +/- 2.1

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001

TABLE 1–2b. Inhaled Corticosteroids vs. Theophylline

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD
Tinkelman, Reed, Nelson, et al. 1993	Theo	93	69	11.9 +/- 2.8
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BDP	102	76	11.9 +/- 2.7

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001

TABLE 1–2c. Inhaled Corticosteroids vs. Nedocromil

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD
Childhood Asthma Management Program Research Group 2000a	Placebo	418	411	9 +/- 2.2
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BUD	311	306	9 +/- 2.1

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001

REFERENCES

Adams RJ, Fuhlbrigge A, Finkelstein JA, Lozano P, Livingston JM, Weiss KB, Weiss ST. Impact of inhaled anti-inflammatory therapy on hospitalization and emergency department visits for children with asthma. *Pediatrics* 2001;107(4):706–11.

Agertoft L, Pedersen S. Effects of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000;343(15):1064–69.

Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88(5):373–81.

Altman LC, Munk Z, Seltzer J, Noonan N, Shingo S, Zhang J, Reiss TF. A placebo-controlled, dose-ranging study of montelukast, a cysteinyl leukotriene-receptor antagonist. Montelukast Asthma Study Group. *J Allergy Clin Immunol* 1998;102(1):50–6.

Baker JW, Mellon M, Wald J, Welsh M, Cruz-Rivera M, Walon-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999;103:414–21.

Bleecker ER, Welch MJ, Weinstein SF, Kalberg C, Johnson M, Edwards L, Rickard KA. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. *J Allergy Clin Immunol* 2000;105(6 Pt 1):1123–9.

Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Busse W, Raphael GD, Galant S, Kalberg C, Goode-Sellers S, Srebro S, Edwards L, Rickard K. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: A randomized clinical trial. *J Allergy Clin Immunol* 2001;107(3):461–8.

Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1403–6.

Childhood Asthma Management Program (CAMP) Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343(15):1054–63.

Connett GJ, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1–3 years. Arch Dis Child 1993;69(3):351-5.

Estimated Disease Severity	Study Duration (weeks)	Lung Function Outcomes			Sx/Meds	Utilization Outcomes	Comments
		FEV_1	PEF	PC20			
Mild or Moderate	48	X	X	X			
Mild or Moderate	48	X	X	X			
Mild or Moderate	52	X	X	X		X	
Mild or Moderate	52	X	X	X		X	

Estimated Disease Severity	Study Duration (weeks)	Lung Function Outcomes			Sx/Meds	Utilization Outcomes	Comments
		FEV_1	PEF	PC20			
Mild or Severe	36	X	X	X	X	X	
Mild or Severe	36	X	X	X	X	X	

Estimated Disease Severity	Study Duration (weeks)	Lung Function Outcomes			Sx/Meds	Utilization Outcomes	Comments
		FEV_1	PEF	PC20			
Mild or Moderate	224	X	X	X	X	X	
Mild or Moderate	224	X	X	X	X	X	

Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA* 1997;277(11):887–91.
DuBuske LM, Grossman J, Dube LM, Swanson LJ, Lancaster JF. Randomized trial of zileuton in patients with moderate asthma: effect of reduced dosing frequency and amounts on pulmonary function and asthma symptoms. Zileuton Study Group. *Am J Manag Care* 1997;3(4):633–40.
Hoekstra MO, Grol MH, Bouman K, Stijnen T, Koeter GH, Kauffman HF, Gerritsen J. Fluticasone propionate in children with moderate asthma. *Am J Respir Crit Care Med* 1996;154(4 Pt 1):1039–44.
Israel E, Cohn J, Dube L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. Zileuton Clinical Trial Group. *JAMA* 1996;275(12):931–6.
Jonasson G, Carlsen KH, Blomqvist P. Clinical efficacy of low-dose inhaled budesonide once or twice daily in children with mild asthma not previously treated with steroids. *Eur Respir J* 1998;12(5):1099–104.
Kemp JP, Skoner DP, Szefler SJ, Walton-Bowen K, Cruz-Rivera M, Smith JA. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. *Ann Allergy Asthma Immunol* 1999 Sep;83(3):231–9.
Kemp JP, Dockhorn RJ, Shapiro GG, Nguyen HH, Reiss TF, Seidenberg BC, Knorr B. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998;133(3):424–8.
Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef O, Santanello N, Michele TM, Reiss TF, Nguyen HH, Bratton DL. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001;108(3):E48.
Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, Becker A. Montelukast for chronic asthma in 6- to 14-year old children: a randomized double-blind trial. Pediatric Montelukast Study Group. *JAMA* 1998;279(15):1181–6.
Konig P. Evidence for benefits of early intervention with non-steroidal drugs in asthma. *Pediatr Pulmonol Suppl* 1997;15:34–9.
Laviolette M, Malmstrom K, Lu S, Chervinsky P, Pujet JC, Peszek I, Zhang J, Reiss TF. Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. *Am J Respir Crit Care Med* 1999;160(6):1862–8.

Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, Kraft M, Fish JE, Peters SP, Craig T, et al. Asthma Clinical Research Network for the National Heart, Lung, and Blood Institute. Long-acting beta2-agonist monotherapy vs. continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285(20):2583–93.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. The Group Health Medical Associates. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332(3):133–8.

Nathan RA, Bernstein JA, Bielory L, Bonuccelli CM, Calhoun WJ, Galant SP, Hanby LA, Kemp JP, Kylstra JW, Nayak AS, O'Connor JP, Schwartz HJ, Southern DL, Spector SL, Williams PV. Zafirlukast improves asthma symptoms and quality of life in patients with moderate reversible airflow obstruction. *J Allergy Clin Immunol* 1998;102(6 Pt 1):935–42.

Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2–5 year old asthmatic children. *Am J Resp Crit Care Med* 2000;162:1500–6.

Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337(20):1405–11.

Pearlman DS, Lampl KL, Dowling PJ Jr., Miller CJ, Bonuccelli CM. Effectiveness and tolerability of zafirlukast for the treatment of asthma in children. *Clin Ther* 2000;22(6):732–47.

Petty TL, Rollins DR, Christopher K, Good JT, Oakley R. Cromolyn sodium is effective in adult chronic asthmatics. *Am Rev Respir Dis* 1989;139(3):694–701.

Reed CE, Offord KP, Nelson HS, Li JT, Tinkelman DG. Aerosol beclomethasone dipropionate spray compared with theophylline as primary treatment for chronic mild or moderate persistent asthma. *J Allergy Clin Immunol* 1998;101:14–23.

Schwartz HJ, Petty T, Dube LM, Swanson LJ, Lancaster JF. A randomized controlled trial comparing zileuton with theophylline in moderate asthma. The Zileuton Study Group. *Arch Intern Med* 1998;158(2):141–8.

Simons FE. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. *N Engl J Med* 1997;337(23):1659–65.

Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, Laessig W, Schuster A, Perez-Frias J, Sekerel BE, Menten J, Leff JA. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr* 2001;138(5):694–8.

Storr J, Lenney CA, Lenney W. Nebulized beclomethasone dipropionate in preschool asthma. *Arch Dis Child* 1986;61(3):270–3.

Tasche MJ, Uijen JH, Bernsen RM, de Jongste JC, van der Wouden JC. Inhaled disodium cromoglycate (DSCG) as maintenance therapy in children with asthma: a systematic review. *Thorax* 2000;55(11):913–20.

Tashkin DP, Nathan RA, Howland WC, Minkwitz MC, Simonson SG, Bonuccelli CM. An evaluation of zafirlukast in the treatment of asthma with exploratory subset analyses. *J Allergy Clin Immunol* 1999;103(2 Pt 1):246–54.

Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92(1):64–77.

van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. The Dutch Chronic Non-specific Lung Disease Study Group. *Am Rev Respir Dis* 1992;146(3):547–54.

Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. The Dutch Paediatric Asthma Study Group. *Am J Respir Crit Care Med* 1997;156(3 Pt 1):688–95.

Weinberger M. Zafirlukast and cromolyn are effective first-line therapies for child asthma. *Ann Allergy Asthma Immunol* 2000;84(6):638–9.

LONG-TERM MANAGEMENT OF ASTHMA IN CHILDREN: SAFETY OF INHALED CORTICOSTEROIDS

Question

What are the long-term adverse effects of chronic inhaled corticosteroid use in children on the following outcomes?

- ***Vertical growth?***
- ***Bone mineral density (BMD)?***
- ***Ocular toxicity?***
- ***Suppression of adrenal/pituitary axis?***

Summary Answer to the Question

Strong evidence from clinical trials following children for up to 6 years suggests that the use of inhaled corticosteroids at recommended doses does not have long-term, clinically significant, or irreversible effects on any of the outcomes reviewed. Inhaled corticosteroids do improve health outcomes for children with mild or moderate persistent asthma, and the potential but small risk of delayed growth is well balanced by their effectiveness (SRE-Evidence A, B). Updated text is recommended for the NAEPP's *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* (EPR-2) incorporating the results of the SRE, but this update does not change the EPR-2 statements.

Rationale for the Question

Inhaled corticosteroids have been proven to be beneficial in the treatment of mild or moderate persistent asthma in children. Because this class of compounds has the potential for producing adverse side effects, however, an SRE on the potential long-term adverse effects would help guide consideration of potential risks and benefits in the therapeutic decisionmaking process.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

To be eligible for consideration in the SRE, each study was required to meet the following criteria:

- It reported on inhaled corticosteroid treatment.
- The treatment duration/observation was at least 1 year.
- For prospective studies:
  - Enrolled only patients younger than 18 years of age.

OR

  - Stratified outcomes for patients younger than 18 years of age and reported baseline demographics for the stratified subgroup.
- For retrospective studies:
  - Enrolled children and/or young adults younger than 40 years of age and indicated that a substantial proportion of the exposure to inhaled corticosteroids had been during childhood.
  - Study design was a comparative clinical trial, cohort study, case control study, or cross-sectional study.
- Reported on a group of at least 25 evaluable, similarly treated asthma patients per study arm.
- For growth outcomes:
  - Studies of short-term growth were restricted to randomized clinical trials.

– Studies of long-term growth were restricted to studies that assessed final attained adult height and controlled for confounding variables.

- For bone density, studies were restricted to controlled trials.
- For subcapsular cataract, clinical series studies were also included.
- For hypothalamic-pituitary-adrenal (HPA) axis function, studies also were included that used a pre-post single-arm design, where baseline HPA axis function was measured before initiation of inhaled corticosteroids.

Summary of Findings

Studies

The SRE addressed the long-term adverse effects of chronic inhaled corticosteroid use in children on four outcomes: vertical growth; bone mineral density; ocular toxicity, including posterior subcapsular cataract and glaucoma; and suppression of adrenal/pituitary axis. (See the key evidence tables at the end of this section for a description of the studies reviewed for vertical growth [three retrospective cohort/studies on final height]; bone-mineral density [two cross-sectional studies and one randomized controlled trial]; and HPA axis function [six studies, including three randomized controlled trials]). The difficulties of systematically assessing adverse effects are well known. Most clinical trials are not designed to specifically address adverse effects and thus may be statistically underpowered and of insufficient duration to detect long-term adverse effects. In addition, the results of this evidence review do not apply to adults. For the adult population, particularly elderly adults, adverse effects may differ qualitatively and quantitatively. For example, although effects on vertical growth are not a concern for adults, ocular toxicity is likely to occur more frequently as age increases.

Results of Studies

The available evidence suggests that the use of inhaled corticosteroids at recommended doses does not have frequent, clinically significant, or irreversible effects on any of the outcomes reviewed. It is possible that chronic use of inhaled corticosteroids initiated in childhood and continued through adulthood might have cumulative effects that increase the relative risk of certain conditions—such as osteoporosis, cataracts, or glaucoma—in later life. However, none of the available studies had sufficient followup duration or numbers of patients to assess this possibility definitively. It is also likely that the probability of adverse effects is related to inhaled corticosteroids dosage. No studies identified in the published literature, however, were designed to test the dose-response relationship of inhaled corticosteroids to adverse effects.

Vertical Growth

The long-term prospective studies on growth involved budesonide, and the retrospective analyses included studies on beclomethasone, but the results have been generalized to all inhaled corticosteroid preparations. Although different preparations and delivery services may have a systemic effect at different doses, all short-term studies of numerous preparations suggest that the effect of inhaled corticosteroids on growth is a drug class effect.

Evidence addressing three measures of vertical growth in children was found: short-term growth velocity measured over a period of 1 year or less, growth velocity and change in height measured over longer duration (4 to 6 years), and final attained adult height. The evidence on short-term growth velocity is from a published meta-analysis, which pooled data from 5 randomized controlled trials representing 855 subjects, with a mean age of 9.5 years (Sharek and Bergman 2000). Evidence on growth velocity and height over a longer period of time is from the CAMP trial, comparing inhaled corticosteroids (budesonide), nedocromil, and placebo in 1,041 children with mild or moderate persistent asthma, who were followed for 4 to 6 years (CAMP 2000). For final attained adult height, evidence is from three retrospective cohort studies that adjusted for the potential confounding factor of parental height (Agertoft and Pedersen 2000; Silverstein et al. 1997; Van Bever et al. 1999). Together, these three studies included a total of 243 patients with asthma treated with inhaled corticosteroids, 154 asthmatic patients who had not been treated with inhaled corticosteroids, and 204 nonasthmatic controls.

Evidence on growth velocity when evaluated during the first year of therapy is consistent in showing a difference in height averaging approximately 1 cm between children treated with inhaled corticosteroids and controls. The magnitude of this change in height ($\approx 0.5 \rightarrow 1.5$ cm) has varied between studies using different inhaled corticosteroid preparations, indicating that either the study design or specific steroid preparation/dose may be important considerations (Doull et al. 1995; Allen et al. 1998; Verberne et al. 1997). In the only trial extending beyond 1 year (CAMP 2000), a difference consistent with this magnitude also occurred during the first year of the study. However, in subsequent long-term followup, the difference in growth velocity was not maintained; all groups had similar growth velocity at the end of treatment. At the end of the 4-to-6-year treatment period, there was still an approximately 1 cm difference in cumulative growth between the study groups, but a slight difference in bone age suggests the potential for catchup for the inhaled corticosteroid group.

The evidence on final adult height appears to be fairly consistent as well. However, this evidence is based on cohort studies that are subject to selection bias and the confounding effects of severity of asthma cannot be adjusted. Some comparisons in these studies also were limited by small sample size. Of the three studies, two showed no difference, and one showed a difference in final attained adult height between inhaled corticosteroid users and nonusers. However, the difference was much less than would be expected if a 1 cm/year growth velocity difference noted in the 1-year studies were maintained over several years.

Bone Mineral Density

The CAMP study followed children with mild or moderate persistent asthma and a mean age of approximately 9 years who were treated for 4 to 6 years with inhaled corticosteroids. This study, with large numbers, randomization, and assessment of longitudinal changes, provides strong evidence that there is no effect of inhaled corticosteroids on bone mineral density (BMD) in the doses given and in the duration in the study (CAMP 2002). One retrospective study of 30 young adults found a significant correlation between BMD and dose of inhaled corticosteroids among female patients (Ip et al. 1994). Such studies are subject to potential confounding because of unmeasured differences between groups that are risk factors for low BMD. In addition, the clinical significance of any observed differences in BMD are unknown. Subtle differences in BMD would not have a clinical impact until they were added to other risk factors such as aging, and it is uncertain whether differences observed during young adulthood would persist into old age.

Posterior Subcapsular Cataract and Glaucoma

Studies that report on the occurrence of posterior subcapsular cataracts consist mostly of small cohorts and cross-sectional studies (Allen et al. 1998; Tinkelman et al. 1993; Agertoft et al. 1998; Simons et al. 1993; Nassif et al. 1987; Abuekteish et al. 1995), with the exception of the CAMP study. The expected incidence rate of subcapsular cataract in any population of normal young children and adults is none. These studies are sufficient to rule out a large effect of inhaled corticosteroids on the short-term incidence of cataract, but they are not capable of detecting a small increase in risk of an event that has a baseline risk of essentially zero. In addition, several of the clinical trials that evaluated development of cataracts were of relatively short duration.

Two of these studies also reported on measurements of ocular pressure (Tinkelman et al. 1993; Nassif et al. 1987). The limited data available show no relationship between glaucoma or increased intraocular pressure and inhaled corticosteroids.

Effect on Hypothalamic-Pituitary-Adrenal Axis Function

Two types of evidence on the effects of inhaled corticosteroids on HPA axis function have been reported: three case reports of iatrogenic Cushing syndrome that were possibly related to inhaled corticosteroids (Zimmerman et al. 1998; Taylor et al. 1999; Priftis et al. 1991; Hollman and Allen 1988) and six controlled clinical trials regarding HPA axis function (Tinkelman et al. 1993; Nassif et al. 1987; Scott and Skoner 1999; Ribeiro 1993; Price et al. 1997; Gonzalez Perez-Yarza et al. 1996). Each study evaluated from one to three different measures of HPA axis function, with followup for at least 1 year after initiation of treatment.

The case reports show that systemic effects can occur in clinically detectable ways, with a strong case for causality indicated in the case studies by the accompanying laboratory tests and response when inhaled corticosteroids were withdrawn. In the controlled clinical studies, four studies of serum control values identified no differences. However, three other studies used more sensitive tests of cortisol, such as 24-hour urinary cortisol, and two showed a statistically significant effect of inhaled corticosteroids. It should be noted that these statistically significant results occur as comparisons of mean values between groups. Few or no patients in most studies produce laboratory values out of the normal range. However, the clinical significance of these more sensitive indicators of adrenal function is unknown.

The results of the case reports appear to be causally attributable to inhaled corticosteroids based on clinical presentation, consistency with laboratory findings, and clinical response to reduction or withdrawal of treatment. Although the studies show that, on average, persons may only have clinically insignificant effects of inhaled corticosteroids on the HPA axis, some individuals may be acutely susceptible to their effects.

Additional Literature/Information

Since the release of the EPR-2, a FDA-based committee convened to review the safety of inhaled corticosteroid therapy, with particular emphasis on growth effects. The FDA committee recommended inserting the following cautionary wording in package inserts for all (both nasal and oral) inhaled corticosteroid medications: "A reduction in growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should follow closely the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed (http://www.fda.gov)."

Two additional studies on the effect of inhaled corticosteroids were completed after the SRE; the studies involved primarily adults but included some children and thus were considered by the Expert Panel. One report pertaining to the risk of cataract formation among patients 3 to 90 years of age was based on a large retrospective cohort study in the United Kingdom-based General Practice Research Database population, with a nested case-control analysis among users of inhaled corticosteroids and patients without previous steroid use who were younger than 90 years of age. All users of inhaled corticosteroids were at a marginally increased risk of cataract formation (risk ratio = 1.3) compared to patients who did not use corticosteroids. Among individuals 40 years of age or older, the risk ratio increased as numbers of inhaled corticosteroid prescriptions increased after controlling for other variables. These trends were not evident for those individuals younger than 40 years of age (Jick et al. 2001).

A prospective cohort study on bone loss in women 18 to 45 years of age reported that bone-density loss at the total hip and the trochanter—but not at the femoral neck or spine—increased with the number of puffs per day of an inhaled corticosteroid (Israel et al. 2001). However, the clinical significance of these findings is uncertain because the rate of loss reported was small, any association of this small loss with increased risk of bone fracture has not been established, and the rates varied among the women taking the inhaled corticosteroids.

Recommendations for EPR Update

Based on this information from the SRE and additional studies, the Expert Panel recommends the following text (noted by shaded text) as an update to pages 71 through 73 of EPR-2 (The Medications, Special Issues on Safety, Systemic Adverse Effects). This text updates—but does not change—the EPR-2 recommendations.

Linear Growth

A reduction in growth velocity in children or adolescents may occur as a result of inadequate control of chronic diseases such as asthma or from the use of corticosteroids for treatment. Overall, however, the available cumulative data in children suggest that, although low-to-medium doses of inhaled corticosteroids may have the potential of decreasing growth velocity, the effects are small, nonprogressive, and may be reversible (SRE-Evidence A, B, C). The long-term prospective studies on growth involved budesonide, and the retrospective analyses included studies on beclomethasone, but the results have been generalized to include all inhaled corticosteroid preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies on numerous preparations suggest that the effect of inhaled corticosteroids on growth is a drug-class effect. When high doses of inhaled corticosteroids are necessary to achieve satisfactory asthma control, the use of adjunctive long-term-control therapy should be initiated in order to reduce the dose of inhaled corticosteroids and thus minimize possible dose-related long-term effects on growth. Physicians should monitor the growth of children and adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression or delay if a child's or an adolescent's growth appears slowed.

Bone Mineral Density

Low-to-medium doses of inhaled corticosteroids appear to have no serious adverse effects on BMD in children (SRE-Evidence A) (CAMP 2000). A small, dose-dependent reduction in BMD may be associated with inhaled corticosteroid use in patients older than 18 years of age (SRE-Evidence C; Evidence B) (Ip et al. 1994; Israel et al. 2001), but the clinical significance of these findings is not clear.

Cataracts

In children, low-to-medium dose inhaled corticosteroid therapy has no significant effects on the incidence of subcapsular cataracts or glaucoma (SRE-Evidence A, C) (CAMP 2000; Jick et al. 2001). High (greater than 2000 mg) cumulative lifetime doses of inhaled corticosteroids may increase slightly the prevalence of cataracts as suggested in two retrospective studies of adult and elderly patients (SRE-Evidence C; Evidence C) (Cumming et al. 1997; Jick et al. 2001).

Hypothalamic-Pituitary-Adrenal Axis Function

The available evidence indicates that, on average, children may experience only clinically insignificant, if any, effects of low-to-medium dose inhaled corticosteroids on the HPA axis (SRE-Evidence A, C). Rare individuals, however, may be more susceptible to their effects even at conventional doses.

Recommendations for Future Research

- What are the long-term effects of inhaled corticosteroid therapy on BMD and cataract formation if it is initiated at a young age and continued for prolonged periods of time?
- Are potential growth effects of inhaled corticosteroid therapy more pronounced during certain developmental periods (e.g., first 3 years of life, preadolescence)?

Key Evidence Tables

TABLE 1–3. Differences in Adult Target Height in Cohort Studies

Study	Group (n) Comparison	Difference in (Adult Target) Height (cm)[1]
Silverstein, Yunginger, Reed et al. 1997	All asthmatics (n = 153) vs. nonasthmatics (n = 153)	0.2
	All corticosteroid users (n = 58) vs. noncorticosteroid asthmatics (n = 95)	-1.2
	Males: All corticosteroid users (n = 30) vs. noncorticosteroid asthmatics (n = 45)	-1.8
	Females: All corticosteroid users (n = 28) vs. noncorticosteroid asthmatics (n = 50)	-0.8
	Oral corticosteroid users (n = 40) vs. never used corticosteroids (n = 95)	-1.4
	Inhaled corticosteroid users (n = 18) vs. never used corticosteroids (n = 95)	-0.9
Van Bever, Desager, Lijssens et al. 1999	All inhaled corticosteroid users (n = 43) vs. never used corticosteroids (n = 42)	-2.54[2]
	Males: Inhaled corticosteroid users (n = 23) vs. never used corticosteroids (n = 26)	-3.09[b]
	Females: Inhaled corticosteroid users (n = 18) vs. never used corticosteroids (n = 95)	-1.99
Agertoft and Pedersen 2000	All inhaled corticosteroid users (n = 142) vs. noncorticosteroid using asthmatics (n = 18)	+0.5
	All inhaled corticosteroid users (n = 142) vs. healthy sibling control group (n = 51)	-0.6
	Males: All inhaled corticosteroid users (n = 86) vs. healthy sibling control group (n = 24)	-0.6
	Females: All inhaled corticosteroid users (n = 56) vs. healthy sibling control group (n = 27)	-0.8

[1] A negative number indicates that corticosteroid users had lower attained adult height than the comparison group, controlling for parental height.
[2] $p < 0.05$.
Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

TABLE 1–4. Effects of Inhaled Corticosteroids on Bone Mineral Density

Citation	Treatment Arm	Number Enrolled	Number Evaluable	Treatment Duration (years)	Bone Density Result	P Value	Comment
Agertoft, Larsen, and Pedersen 1998	Budesonide 504 mcg per day	157	157	3.0 (minimum)	Total body BMD: 0.92 g/cm^2		No significant difference between groups or between boys and girls in bone mineral capacity or total bone calcium
	Nonsteroid asthma therapies	111	111	3.0 (minimum)	Total body BMD: 0.92 g/cm^2	NS	Mean treatment time 4.4 (3–6) years
Ip, Lam, Yam, et al. 1994	Beclomethasone or budesonide	30	30	3.3	Spine: 0.944 Femur Neck: 0.769 Trochanter: 0.676 Ward's Triangle: 0.729	0.041 0.007 0.034 0.016	Stratified by sex, all differences significant for females but not for males
	Normal control subjects, matched by sex, age, BMI, menopausal status	30	30	NA	Spine: 0.944 Femur Neck: 0.769 Trochanter: 0.676 Ward's Triangle: 0.729		
Childhood Asthma Management Program Research Group 2000a	Budesonide 400 mcg/day	311	311	4–6 yr	Change in spine BMD: 0.17 g/cm^2	0.53 vs. placebo	
	Nedocromil 16 mg/day	312	312	4–6 yr	Change in spine BMD: 0.17 g/cm^2	0.15 vs. placebo	
	Placebo	418	418	4–6 yr	Change in spine BMD: 0.18 g/cm^2		

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

TABLE 1–5. Effects of Inhaled Corticosteroids on HPA Function

Citation	Treatment Arms	Measure of HPA Axis Function
Randomized Clinical Trials		
Scott and Skoner 1999	BUD 500 mcg/day (n = 132) vs. conventional treatment (n = 57)	Serum cortisol at baseline and 12 mo.
		ACTH-stimulated cortisol at baseline and 12 mo.
		% patients from normal to abnormal stimulation test between baseline and 12 mo.
Price, Russell, Hindmarsh, et al. 1997	FP 50 mcg/day (n = 36) vs. cromolyn 20 mg/day (n = 27)	Urinary cortisol geometric mean ratio between patient groups at 6 and 12 mo.
Tinkelman, Reed, Nelson et al. 1993	BDP 84 mcg/day (n = 102) vs. theophylline (n = 93)	Serum cortisol at baseline, 6 and 12 mo.
		ACTH-stimulated cortisol at baseline, 6 and 12 mo.
Cross-section studies		
Gonzales Perez-Yarza, Mintegui, Garmendia, et al. 1996	Budesonide or beclomethasone, mean dose 676 +/- 280 mcg/day (range, 226–1800) (n = 250) vs. normal controls (n = 108)	Urinary cortisol
		No. of abnormal ACTH stimulation tests in subset with urinary cortisols below 1 standard deviation
Nassif, Weinberger, Sherman, et al. 1987	Beclomethasone 358 mcg/day (n = 17) vs. Beclomethasone 726 mcg/day (n = 14) vs. asthmatic control group (n = 20) and normal control groups (n = 21)	Serum cortisol
		Urinary cortisol
Single arm pre-post study		
Ribiero 1993	Budesonide 200 mcg/day (n = 47)	Serum cortisol at baseline and 12 mo.
		ACTH-stimulated cortisol at baseline and 12 mo.

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Results	P-Value	Comments
BUD (0, 12 mo.): 320, 300 Conventional (0, 12 mo.): 250, 315	"No significant differences"	Subset of full trial
BUD (0, 12 mo.): 695, 655 Conventional (0, 12 mo.): 690, 720	"No significant differences"	Subset of full trial
BUD: 24% Conventional: 21%	"Not different"	
Ratio of urinary cortisol at 6 mo.: 0.85 Ratio of urinary cortisol at 12 mo.: 0.96	NS: 95% CI includes 1 NS: 95% CI includes 1	
BDP 336 mcg/day (0, 6, 12 mo.): 328, 306, 309 Theophylline (0, 6, 12 mo.): 309, 322, 334	Not stated: "similar"	
BDP 336 mcg/day (baseline): 726 (6, 12 mo. NA) Theophylline (baseline): 723 (6, 12 mo. NA)	Not stated: "almost identical"	
BUD/BDP: 58.69 nmol/m^2/day Control: 81.98 nmol/m^2/day	$p < 0.05$	
BUD/BDP group: 2 abnormal tests (3.1%) Control group: Not done	Not applicable	One of the two patients with abnormal test had chronic oral corticosteroids.
BDP <450 mcg/day: 403 BDP >450 mcg/day: 353 Asthmatic controls: 353 Normal controls: 367	Not specifically stated: presumed NOT statistically significant	
BDP <450 mcg/day: 22 mcg/g creatinine BDP >450 mcg/day: 16.5 mcg/g creatinine Asthmatic controls: 43 mcg/g creatinine Normal controls: 29.5 mcg/g creatinine	Test: "Statistically significant" from controls	
Basal cortisol (0, 12 mo.): 497, 497	Not stated, presumed not statistically significant	
4-hr. stimulated cortisol (0, 12 mo.): 1104, 1131 5-hr. stimulated cortisol (0, 12 mo.): 1242, 1380	$p = 0.02$ for increase from baseline, both tests	

REFERENCES

Abuekteish F, Kirkpatrick JN, Russell G. Posterior subcapsular cataract and inhaled corticosteroid therapy. *Thorax* 1995;50(6):674–6.

Agertoft L, Larsen FE, Pedersen S. Posterior subcapsular cataracts, bruises and hoarseness in children with asthma receiving long-term treatment with inhaled budesonide. *Eur Respir J* 1998;12(1):130–5.

Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000;343(15):1064–9.

Allen DB, Bronsky EA, LaForce CF, Nathan RA, Tinkelman DG, Vandewalker ML, Konig P. Growth in asthmatic children treated with fluticasone propionate. Fluticasone Propionate Asthma Study Group. *J Pediatr* 1998;132(3 Pt 1):472–7.

Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Childhood Asthma Management Program (CAMP) Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343(15):1054–63.

Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997;337(1):8–14.

Doull IJ, Freezer NJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;151(6):1715–19.

Gonzalez Perez-Yarza E, Mintegui J, Garmendia A, Callen M, Reguilon MJ, Garrido A, Emparanza JI. The excretion of free cortisol in the urine in healthy children and in asthmatics treated with long-term inhaled glucocorticoids. *An Esp Pediatr* 1996;44(6):531–6.

Hollman GA, Allen DB. Overt glucocorticoid excess due to inhaled corticosteroid therapy. *Pediatrics* 1988;81(3):452–5.

Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest* 1994;105(6):1722–7.

Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, LeBoff MS. Effects of inhaled glucorticoids on bone density in premenopausal women. *N Engl J Med* 2001;345(13):941–7.

Jick SS, Vasilakis-Scaramozza C, Maier WC. The risk of cataract among users of inhaled steroids. *Epidemiology* 2001;12(2):229–34.

Nassif E, Weinberger M, Sherman B, Brown K. Extrapulmonary effects of maintenance corticosteroid therapy with alternate-day prednisone and inhaled beclomethasone in children with chronic asthma. *J Allergy Clin Immunol* 1987;80(4):518–29.

Price JF, Russell G, Hindmarsh PC, Weller P, Heaf DP, Williams J. Growth during one year of treatment with fluticasone propionate or sodium cromoglycate in children with asthma. *Pediatr Pulmonol* 1997;24(3):178–86.

Priftis K, Everard ML, Milner AD. Unexpected side-effects of inhaled steroids: a case report. *Eur J Pediatr* 1991;150(6):448–9.

Ribeiro LB. Budesonide: safety and efficacy aspects of its long-term use in children. *Pediatr Allergy Immunol* 1993;4(2):73–8.

Scott MB, Skoner DP. Short-term and long-term safety of budesonide inhalation suspension in infants and young children with persistent asthma. *J Allergy Clin Immunol* 1999;104(4 Pt 2):200–9.

Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. *Pediatrics* 2000;106(1):E8.

Silverstein MD, Yunginger JW, Reed CE, Petterson T, Zimmerman D, Li JT, O'Fallon WM. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol* 1997;99(4):466–74.

Simons FE, Persaud MP, Gillespie CA, Cheang M, Shuckett EP. Absence of posterior subcapsular cataracts in young patients treated with inhaled glucocorticoids. *Lancet* 1993;342(8874):776–8.

Taylor DA, Jensen MW, Kanabar V, Engelstatter R, Steinijans VW, Barnes PJ, O'Connor BJ. A dose-dependent effect of the novel inhaled corticosteroid ciclesonide on airway responsiveness to adenosine-5'-monophosphate in asthmatic patients. *Am J Respir Crit Care Med* 1999;160(1):237–43.

Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92(1):64–77.

Van Bever HP, Desager KN, Lijssens N, Weyler JJ, Du Caju MV. Does treatment of asthmatic children with inhaled corticosteroids affect their adult height? *Pediatr Pulmonol* 1999;27(6):369–75.

Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. The Dutch Paediatric Asthma Study Group. *Am J Respir Crit Care Med* 1997(3 Pt 1);156:688–95.

Zimmerman B, Gold M, Wherrett D, Hanna AK. Adrenal suppression in two patients with asthma treated with low doses of the inhaled steroid fluticasone propionate. *J Allergy Clin Immunol* 1998;101(3):425–6.

COMBINATION THERAPY: ADDITION OF OTHER LONG-TERM-CONTROL MEDICATIONS TO INHALED CORTICOSTEROIDS

Question

In patients with moderate persistent asthma who are receiving inhaled corticosteroids, does addition of another long-term-control agent improve outcomes?

Summary Answer to the Question

Strong evidence consistently indicates that long-acting inhaled beta$_2$-agonists added to low-medium-dose inhaled corticosteroids improve outcomes (SRE-Evidence A). Adding a leukotriene modifier or theophylline to inhaled corticosteroids or doubling the dose of inhaled corticosteroids also improves outcomes, but the evidence is not as substantial (SRE-Evidence B). The NAEPP EPR-2 recommendations for moderate persistent asthma have been revised: The preferred treatment for adults and children older than 5 years of age is the addition of long-acting inhaled beta$_2$-agonists to low-to-medium doses of inhaled corticosteroids. Adjunctive therapy combinations have not been studied in children younger than 5 years of age. For this age group, it is the opinion of the Expert Panel that there are two preferred options for treating moderate asthma: either the addition of long-acting inhaled beta$_2$-agonists to a low dose of inhaled corticosteroids or medium-dose inhaled corticosteroids as monotherapy.

Rationale for the Question

There are an increased number of studies evaluating combination therapy primarily as a result of the development of fixed-dose combinations of the long-acting inhaled beta$_2$-agonists and inhaled corticosteroids (salmeterol plus fluticasone proprionate, now FDA-approved, and formoterol plus budesonide, under development). The ongoing preference to minimize the dose of corticosteroids, especially for patients taking high doses, and to reduce the possibility of adverse side effects, has stimulated studies of adjunctive therapies. The question of interest is whether, for patients requiring more than low doses of inhaled corticosteroids, equal or better asthma control could be achieved by adding an additional medication rather than by increasing the dose of inhaled corticosteroids. An extensive body of literature addressing the question of adjunctive therapy has become available since the publication of EPR-2 and has thus warranted Expert Panel Review.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

The SRE divided the studies into three study design categories:

1. The addition of a long-term-control medication to a fixed dose of inhaled corticosteroids compared with the same dose of inhaled corticosteroids alone. This design simply assesses whether combination therapy is better than monotherapy with inhaled corticosteroids. The potential bias from this study design is seen when patients can be controlled on inhaled corticosteroids alone, resulting in a negative study because of the inability to improve.
2. The addition of a long-term-control medication to inhaled corticosteroids with subsequent downward titration of the dose of inhaled corticosteroids to the lowest dose that maintains control. This design is even more problematic because it may be raising a fundamentally different question—i.e., "Can the other long-term-control medication act as a substitute for the inhaled corticosteroids following initial control of the asthma?" However, if the goal is simply to lower the dose of inhaled corticosteroids by some increment (usually half), then the study design addresses the primary question more directly.
3. The addition of the long-term-control medication compared with increasing the dose of inhaled corticosteroids to improve asthma control. This design most directly addresses the question, because eligible patients first demonstrated a lack of adequate control during an open run-in period on inhaled corticosteroids. The definition of inadequate control varied among studies, however, and this variance could introduce some bias.

In addition to the eligibility criteria for selecting studies related to all topics in the SRE (described in the Introduction), the criteria for selecting studies for this question were as follows:

- Study comparisons included:
  - Inhaled corticosteroids alone compared to inhaled corticosteroids plus leukotriene modifiers, or long-acting beta$_2$-agonists, or theophylline

OR

  - Two different long-term-control medications in patients using inhaled corticosteroids

OR

  - The addition of an alternative medication to an increased dose of inhaled corticosteroids for patients already on inhaled corticosteroids.
- Treatment duration was at least 4 weeks.
- At least 90 percent of patients in the study were on inhaled corticosteroids, or the subgroup of patients on inhaled corticosteroids was analyzed separately, and this subgroup otherwise met the eligibility criteria for this question.
- No more than 10 percent of the patients in the population or in a subgroup were on oral corticosteroids.

Summary of Findings

Studies

The majority of the studies reviewed by the SRE fit into study design categories 1 and 3. Thirty-nine studies involving 45 comparisons and a total of 9,020 patients were selected for the SRE. (See the key evidence tables in this section.) Overall, 34 of the 45 comparisons evaluated the addition of a long-acting beta$_2$-agonist to inhaled corticosteroids. All but one of the studies were randomized trials. The following comparisons were made:

- Twenty-six compared the addition of a drug to a fixed dose of inhaled corticosteroids (18 [3,163 patients] compared long-acting inhaled beta$_2$-agonists; 4 [234 patients] compared theophylline, and 4 [885 patients] compared LTRAs).
- Four compared a titrated dose of inhaled corticosteroids after the addition of a drug (3 [268 patients] compared long-acting inhaled beta$_2$-agonists; 1 [226 patients] compared LTRA).
- Fifteen compared a low-to-moderate dose of inhaled corticosteroids with an additional drug to high-dose inhaled corticosteroids (13 [4,285 patients] compared long-acting inhaled beta$_2$-agonists and 2 [252 patients] compared theophylline).
- No studies were found that compared long-acting oral beta$_2$-agonists.
- No studies meeting SRE quality criteria were found that compared the addition of cromolyn or nedocromil.

Results of Studies

Addition of long-acting inhaled beta$_2$-agonists

A sufficient number of quality studies in both design categories 1 and 3 were completed to enable meta-analyses of lung function and as-needed short-acting beta$_2$-agonist use outcomes in each category. (See the key evidence tables in this section for a description of eligible studies.) Both the systematic review and meta-analyses confirmed the superiority of combination therapy to inhaled corticosteroids monotherapy. In particular, the findings of the meta-analysis for the addition of long-acting inhaled beta$_2$-agonist compared with increasing the inhaled corticosteroid dosage were consistent with a previously reported meta-analysis (Shrewsbury et al. 2000). In addition to similar findings on lung function, Shrewsbury and colleagues had access to the original data and were able to assess the rate of asthma exacerbations, reporting a positive benefit of the combination therapy. The data are robust and convincing that the addition of long-acting inhaled beta$_2$-agonists to inhaled corticosteroids improves lung function and asthma control in patients inadequately controlled with low-to-medium doses of inhaled corticosteroids.

Of note is the paucity of pediatric trials in the database. One pediatric study by Verberne et al. (1998) was completed in older children (mean 11 years of age). Following a 6-week run-in, 120 patients were randomized to either low-dose inhaled corticosteroid—beclomethasone dipropionate (BDP) (400 mcg/day), medium-dose BDP (800 mcg/day), or low-dose BDP plus the long-acting inhaled beta$_2$-agonist salmeterol for 1 year. No significant difference was found among any of the three arms in postbronchodilator FEV_1 or PC20 FEV_1 methacholine provocation. These results suggest that the children were adequately controlled with low-dose inhaled corticosteroids and that the addition of the long-acting inhaled beta$_2$-agonist neither improved nor worsened airway responsiveness. Thus, due to the design, this study cannot refute the potential benefit of the drug combination for those children inadequately controlled on low-dose inhaled corticosteroids alone.

A multicenter double-blind trial of salmeterol as added therapy for children who were not well controlled with inhaled corticosteroids (mean dose of 750 mcg/day) demonstrated significant improvement in morning PEF and symptom-free days in the long-acting inhaled beta$_2$-agonist plus inhaled corticosteroid group, compared to the placebo plus inhaled corticosteroid group (Russell 1995). Although this study did not compare the addition of a long-acting inhaled beta$_2$-agonist to an increased dose of inhaled corticosteroids, the patients were already receiving doses of inhaled corticosteroids ranging from 400 to 2,400 mcg a day. Thus, this study established a need for further asthma control in children already receiving inhaled corticosteroids; it also more directly addresses the question posed by the SRE.

Addition of long-acting oral beta$_2$-agonists

No studies were found.

Addition of cromolyn/nedocromil

No studies meeting the quality criteria of the SRE were found. No new studies since the publication of the EPR-2 were found.

Addition of theophylline

Six studies evaluated the addition of theophylline, including two more recent studies that compared the addition to increased inhaled corticosteroid dosage. The results indicate that the combination of drugs and the increased dose of the inhaled corticosteroids result in equivalent outcomes, suggesting that theophylline has only a modest steroid-sparing effect. None of the four studies (two in children 6 to 19 years of age) comparing the addition of theophylline to a fixed dose of inhaled corticosteroids met the quality criteria of the SRE, because all had study-design and statistical problems. No studies were found that included children younger than 6 years of age.

Addition of leukotriene modifiers

Five published studies evaluated the addition of leukotriene modifiers to fixed doses of inhaled corticosteroids; none compared the combination to increasing the dose of inhaled corticosteroids. Two of these studies used pranlukast, an LTRA unavailable in the United States, and one used zafirlukast in a dose four times the dosage recommended on the package label. None of the studies included children younger than 12 years of age. The most relevant of the five studies (Laviolette et al. 1999), which contributed the most patients and had the longest duration, failed to meet the definition of high quality for the SRE because it met only one of the quality indicators (double blinding). Limitations of these studies preclude definitive conclusions, but they reveal a trend showing improvement in lung function and, in some, symptoms from the combination of leukotriene modifiers and inhaled corticosteroids compared with a fixed dose of inhaled corticosteroids alone.

Addition of an adjunctive agent and down titration of the inhaled corticosteroids

This group of studies is discussed separately, as some of the trials were designed to ask a fundamentally different question (i.e., could the adjunctive therapy ultimately replace inhaled corticosteroid therapy?). An example is the study that attempted to wean patients from the inhaled corticosteroids after beginning a long-acting inhaled beta$_2$-agonist until they had an exacerbation or the inhaled corticosteroid therapy was discontinued (McIvor et al. 1998). Ten of the 13 patients in the long-acting inhaled beta$_2$-agonist arm experienced an exacerbation only after discontinuing their inhaled corticosteroids, providing further evidence that the long-acting inhaled beta$_2$-agonist should not be used as a substitute for anti-inflammatory therapy. One trial attempted to wean patients from the inhaled corticosteroids after addition of the LTRA montelukast, with the goal of maintaining adequate asthma control (Lofdahl et al. 1999). The mean percentage reduction in the dose of inhaled corticosteroids was 47 percent—a 17 percent increase over placebo—and 40 percent of patients were able to discontinue their inhaled corticosteroids compared with 29 percent in the placebo arm, which was not statistically significant. Thus, data are inconclusive about the "steroid sparing" effect of adjunctive therapy, and data show that patients cannot be entirely weaned from inhaled corticosteroids. In addition, data from these studies are insufficient to determine the relative "steroid-sparing" effect of the various adjunctive therapies. Finally, none of the studies included children younger than 5 years of age.

Additional Literature/Information

In addition to reviewing studies published after the SRE, the Expert Panel considered four other issues relevant to the question of the use of combination therapy for the treatment of persistent asthma: the effect of the different combinations on the rate of exacerbations of asthma; the comparison of different combinations to determine relative effectiveness; the use of combination therapy in children 5 years of age and younger; and the use of combination therapy in severe persistent asthma.

Studies Published After the SRE

The addition of montelukast to inhaled corticosteroids was evaluated in 279 children 6 to 14 years of age with moderate asthma whose symptoms were not completely controlled on 400 mcg budesonide daily (Simons et al. 2001). This study was a double-blinded, randomized, placebo-controlled, crossover trial with a 4-week open-label run-in period to establish the need for adjunctive therapy. Each treatment period also consisted of 4 weeks. The trial had sufficient power (95 percent) to detect a 4.4-percent difference between the placebo and the active drug in the primary end point, FEV_1 percent predicted. In the intention-to-treat analysis, no significant difference was found between the placebo and montelukast for the primary end point (1.3 percent difference). A post hoc censure of the data revealed a statistically significant 1.9 percent difference between the active drug and the placebo. Other significant differences reported in favor of montelukast were a decrease in beta$_2$-agonist usage (.33 puffs/day difference) and exacerbation days that also were defined by beta$_2$-agonist usage—an improvement in morning and evening PEFs (9.7 L/min and 10.7 L/min, respectively). It was not indicated whether these were intention-to-treat analyses. Outcomes found to be the same at the end of the study included worsening asthma, global evaluations, number of asthma attacks requiring intervention, and quality of life.

Another study compared the addition of theophylline to low-dose BDP (400 mcg daily) with increasing the dose of BDP to 1,000 mcg daily or maintaining patients on the low-dose BDP alone for 7 months (Lim et al. 2000). The study found no difference between the high-dose inhaled corticosteroids and the theophylline group for any outcome, thus confirming the SRE findings.

Effect of Combination Therapy on the Rate of Exacerbations of Asthma

Reduction in the rate of asthma exacerbations has been suggested as a surrogate for an anti-inflammatory effect. Compared with placebos, leukotriene modifiers have been reported to reduce the number of exacerbations treated with prednisone (zileuton, zafirlukast, and montelukast package inserts). Both of the long-acting inhaled beta$_2$-agonists—formoterol and salmeterol—have been reported to reduce exacerbations of asthma when administered in conjunction with inhaled corticosteroids (Pauwels et al. 1997; Shrewsbury et al. 2000). In one study, the addition of formoterol to either low-dose (100 mcg bid) or high-dose (400 mcg bid) budesonide significantly reduced both mild and severe exacerbations. Further, fewer exacerbations occurred in the high-dose inhaled corticosteroid group compared with the lower dose group, though statistical analysis was not done (Pauwels et al. 1997). A meta-analysis of studies in which the addition of salmeterol to a lower dose of inhaled corticosteroids was compared with a higher dose of inhaled corticosteroids demonstrated that exacerbations were significantly lower with the combination therapy (Shrewsbury et al. 2000).

It has been suggested that this reduction in exacerbations may be attributed to an enhanced corticosteroid effect due to priming of the glucocorticoid receptor by the long-acting inhaled beta$_2$-agonist (Eickelberg et al. 1999). Two recently published studies (Lazarus et al. 2001; Lemanske et al. 2001) also are pertinent to the issue of using asthma exacerbation as an outcome. In the first trial, those patients adequately controlled on low-dose inhaled corticosteroids were left on the inhaled corticosteroids, switched to the long-acting beta$_2$-agonist salmeterol, or switched to placebo. Although the conventional outcomes (morning and evening PEFs) for the salmeterol and inhaled corticosteroid arms were not different, the salmeterol group had a significantly greater number of exacerbations and treatment failures—again demonstrating that the long-acting inhaled beta$_2$-agonists cannot substitute for inhaled corticosteroids (Lazarus et al. 2001). The companion study evaluated the ability to reduce the dose of inhaled corticosteroids following the introduction of a long-acting inhaled beta$_2$-agonist in those patients initially suboptimally controlled on the inhaled corticosteroids (Lemanske et al. 2001). In this group, the dose of inhaled corticosteroids was reduced by one-half in those patients responding to the addition without any significant change in asthma control, yet a significant treatment failure rate was noted when the inhaled corticosteroids were stopped.

Although clinical studies in the SRE suggest that the addition of a long-acting inhaled beta$_2$-agonist to a low-to-medium dose of inhaled corticosteroids is the most effective treatment for moderate persistent asthma (step 3 care), there may be situations where both the addition of a long-acting inhaled beta$_2$-agonist and an increase in the dose of inhaled corticosteroids are indicated. The studies of Sont et al. (1999) and Pauwels et al. (1997) support the added benefit of a higher dose of inhaled corticosteroids in reducing asthma exacerbations. Thus, for patients considered to be at higher risk for exacerbations (suggested by a history of repeated short courses of prednisone, emergency department visits, or hospitalizations), both the addition of a long-acting inhaled beta$_2$-agonist and an increase in the dose of inhaled corticosteroids may be indicated.

Comparison of Combinations To Determine Relative Effectiveness

Not included in the SRE were direct comparative studies of the effectiveness of the various drugs used as adjuncts to inhaled corticosteroids. Studies comparing the long-acting inhaled beta$_2$-agonist to sustained-release theophylline are numerous (Davies et al. 1998), and generally involve patients receiving inhaled corticosteroids. A meta-analysis of these studies (Davies et al. 1998) demonstrated that both pulmonary function and asthma symptoms showed more improvement with the long-acting inhaled beta$_2$-agonist as adjunctive therapy than with theophylline. In the three published studies included in the meta-analysis, between 50 percent and 97 percent of the subjects were receiving regular inhaled corticosteroid therapy (Fjellbirkeland et al. 1994; Muir et al. 1992; Paggiaro et al. 1996).

A comparison of the addition of the long-acting beta$_2$-agonist salmeterol to the addition of the LTRA zafirlukast (Busse et al. 1999) also examined a mixed population; however, this study was not included in the SRE because more than 80 percent of the patients in both arms were using inhaled corticosteroids, rather than 90 percent required by the SRE selection criteria. The study otherwise met the criteria for a high-quality study and should be considered. The results indicate that salmeterol improved both pulmonary function and asthma symptoms significantly more than did zafirlukast.

Another direct comparison of long-acting inhaled beta$_2$-agonists and a leukotriene modifier as combination therapy was published after the SRE (Nelson et al. 2000). This study also met the SRE criteria for high quality and should be considered. The investigators evaluated patients who were still symptomatic on low-dose inhaled corticosteroids (fluticasone 88 mcg bid), before and after the addition of the long-acting beta$_2$-agonist salmeterol or the LTRA montelukast over 3 months. Those patients receiving salmeterol plus fluticasone, compared with those on montelukast and fluticasone, had greater improvement in pulmonary function and in some asthma symptoms, and experienced significantly fewer exacerbations.

Although the addition of sustained-release theophylline or a leukotriene modifier to treatment with inhaled corticosteroids generally is not as effective as the addition of a long-acting inhaled beta$_2$-agonist, there may be circumstances when these combinations would be indicated for selected patients. Among the considerations favoring one of these alternative combinations would be the patient's intolerance of the side effects of the long-acting inhaled beta$_2$-agonist, marked preference for oral therapy, demonstration of superior responsiveness to the alternate class of drug, as well as financial considerations (theophylline is the least expensive). Finally, although the recently marketed fixed-dose combination of fluticasone propionate and salmeterol in a DPI may provide an advantage in terms of ease of use (one inhaler instead of two), there is no evidence of superiority of this particular combination over that of other inhaled corticosteroids and long-acting inhaled beta$_2$-agonists.

Combination Therapy in Children 5 Years of Age and Younger

None of the adjunctive therapy combinations have been adequately studied in children 5 years of age and younger. Indeed, only one study, a study adding the long-acting inhaled beta$_2$-agonist salmeterol to inhaled corticosteroids, included patients as young as 4 years of age (Russell 1995). The lower age limit of all other combination therapy studies in children is 6 years of age (Simons et al. 2001; Meltzer et al. 1992; Nassif et al. 1981). The data are thus inadequate to provide definitive recommendations on combination therapy in young children, and recommendations must be extrapolated from studies in older children and adults, which support the combination of inhaled corticosteroids and long-acting inhaled beta$_2$-agonists. Because patients in this age range may be at greater risk for systemic effects from high doses of inhaled corticosteroids, the use of combination therapy seems prudent when goals of therapy are not attained with low or the lower range of medium doses of inhaled corticosteroids. However, as noted in the section on effectiveness of long-term-control medications, there are no data available on the use of long-acting inhaled beta$_2$-agonists in infants and young children, whereas studies of medium doses of inhaled corticosteroids demonstrate effectiveness in this age group.

The following medications have been FDA-approved for young children: the inhaled corticosteroids budesonide nebulizer solution approved for children 1 to 8 years of age and fluticasone DPI approved for children 4 years of age and older; the long-acting inhaled beta$_2$-agonist salmeterol DPI approved for children 4 years of age and older; and, based on safety data rather than efficacy data, the LTRA montelukast 4 mg chewable approved for children 2 to 6 years of age.

Combination Therapy in Patients With Severe Persistent Asthma

Current recommendations for treatment include adding oral systemic corticosteroids if a patient cannot achieve and maintain control with high doses of inhaled corticosteroids and long-acting bronchodilators. An alternative approach may be to add a third long-term-control medication to a combination of medium-to-high-dose corticosteroids and long-acting inhaled beta$_2$-agonists in severe persistent asthma. However, few trials regarding this approach and of sufficient quality are available. A double-blind, crossover trial of LTRA (10 mg montelukast or placebo) in 72 adults with severe persistent asthma found no benefit from the addition of montelukast to other medication (Robinson et al. 2001). In this study, the concurrent medication varied among the patients: All patients received medium-to-high-dose inhaled corticosteroids; 85 percent also received either theophylline, a long-acting inhaled beta$_2$-agonist, or both; and 47 percent also received oral systemic corticosteroids. No attempt was made to eliminate the oral corticosteroids. The treatment period of 14 days for LTRA and 14 days for placebo was relatively short, although leukotriene modifiers usually produce a rapid response. This study indicates that there is no additional benefit to adding LTRA as a third medication. Similar controlled clinical trials have not been conducted to evaluate other long-term-control medications added to the combination of medium-to-high doses of inhaled corticosteroids and long-acting inhaled beta$_2$-agonists in severe persistent asthma. Until more research is conducted, recommendations for managing severe persistent asthma are based on extrapolations from studies of the combination of inhaled corticosteroids and one other long-term-control medication in treating moderate persistent asthma.

Recommendations for EPR Update

Based upon the assessment of evidence provided by the SRE and the additional evidence considered by the Expert Panel, the following changes to step 3 care in EPR-2 are recommended:

- The preferred treatment for those adults and children older than 5 years of age whose asthma is inadequately controlled on low-dose inhaled corticosteroids is combination therapy: the addition of a long-acting inhaled beta$_2$-agonist (SRE-Evidence A) to a low-to-medium dose of inhaled corticosteroids. Scientific evidence from studies of children older than 12 years of age and adults indicates that patients with moderate persistent asthma benefit from two different types of daily medication in order to achieve and maintain optimal control of their asthma: (1) medication aimed at suppressing underlying airway inflammation and (2) a medication whose primary action is bronchodilation. This approach is preferred to increasing the dose of inhaled corticosteroids.

  The exception is indicated for those patients who experience recurring severe exacerbations that require oral prednisone, emergency department visits, or hospitalizations. For these patients, increasing the dose of inhaled corticosteroids along with the addition of a long-acting inhaled beta$_2$-agonist should be considered (SRE-Evidence B).

  For children 5 years of age or younger, combination therapy has not been adequately studied. Therefore, recommendations for step 3 care for this age group are based on extrapolations of data from older children and adults, as well as expert opinion. For children 5 years of age and younger with moderate persistent asthma, there are two equally preferred options: low-dose inhaled corticosteroids and a long-acting beta$_2$-agonist (Evidence B, extrapolation from studies in older children and adults) OR inhaled corticosteroids as monotherapy with an increase of the dose within the medium-dose range (Evidence D).
- Alternative—but not preferred—approaches that may be considered include doubling the dose of inhaled corticosteroids within the medium-dose range (this is an alternative but not preferred option for older children and adults; for children 5 years of age and younger, increasing the inhaled corticosteroid dose is an equally preferred option); adding sustained-release theophylline; or adding a leukotriene modifier (SRE-Evidence B). Leukotriene modifiers or theophylline may be considered if the patient displays intolerance of long-acting inhaled beta$_2$-agonists, has a marked preference for oral therapy, and demonstrates superior responsiveness to the alternative class of drug through a therapeutic trial. Other issues may include financial considerations (theophylline is the least expensive).
- The recommendations for the use of nedocromil and long-acting oral beta$_2$-agonists as alternatives to increasing the dose of inhaled corticosteroids are untenable at this time due to lack of data and should be removed as therapeutic options.

Specifically, the Expert Panel recommends that step 3 in figure 3–4b, Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age, be revised as follows with the revision noted in shaded text. (See Medications: Effectiveness in Children for recommendations for revisions to step 3 in figure 3–6, stepwise approach for managing asthma in children 5 years of age and younger.)

Figure 3–4b. Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age: Treatment (pages 84 through 85 in EPR-2)

Step 3: Moderate Persistent (preferred treatments are in bold print)

Daily Medication:

- Preferred treatment
  - **Low-to-medium-dose inhaled corticosteroids and long-acting inhaled beta$_2$-agonists**
- Alternative treatment (listed alphabetically)
  - Increase inhaled corticosteroids within medium-dose range

OR

  - Low-to-medium-dose inhaled corticosteroids and either a leukotriene modifier OR theophylline
- If needed (particularly in patients with recurring severe exacerbations)
  - **Preferred treatment: Increase inhaled corticosteroids within medium-dose range and add a long-acting beta$_2$-agonist**

  Alternative treatment:
  - Increase inhaled corticosteroids within medium-dose range and add either a leukotriene modifier OR theophylline

Step 4: Severe Persistent

Daily Medication:

- High-dose inhaled corticosteroids

AND

- Long-acting inhaled beta$_2$-agonists

IF NEEDED

- Corticosteroid tablets or syrup long term (1 to 2 mg/kg/day; generally do not exceed 60 mg/day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)

The text in EPR-2 on pages 93 and 94 regarding step 3 and step 4 care for adults and children older than 5 years of age should be revised as follows, with revisions noted by shaded text. (See Medications: Effectiveness in Children for revisions to step 3 for children younger than 5 years of age.)

Step 3: Moderate Persistent Asthma

Consultation with an asthma specialist may be considered because the therapeutic options at this juncture pose a number of challenging risk-benefit outcomes. Before increasing therapy, however, the clinician should review the patient's inhaler technique and adherence, as well as determine whether environmental factors are contributing to the patient's worsening asthma. If a step-up in therapy is required, there are at least four options for initiating step 3 therapy.

- **Add a long-acting inhaled beta$_2$-agonist to a low-to-medium dose of inhaled corticosteroids** (SRE-Evidence A, B). *This is the preferred treatment.* Early investigations suggested that the addition of a long-acting inhaled beta$_2$-agonist to a low (Greening et al. 1994) or medium (Woolcock et al. 1996) dose of inhaled corticosteroids resulted in greater improvement in lung function and overall asthma control than doubling the dose of inhaled corticosteroids. Since that time, numerous studies have confirmed the superiority of combination therapy over increasing the dose of inhaled corticosteroids, even for reducing severe asthma exacerbations (SRE 2001, Shrewsbury et al. 2000). Use of combination therapy has not been shown to mask worsening of inflammation and asthma. Indeed, the combination has consistently been shown to reduce the number of severe asthma exacerbations (Pauwels et al. 1997; Shrewsbury et al. 2000). This approach has proved so successful that it has spawned the development of two fixed-dose combinations of long-acting inhaled beta$_2$-agonists and inhaled corticosteroids in one inhaler, one currently marketed. The fixed-dose combination may be easier to use and hence facilitate adherence to the regimen, but there is no evidence of clinical superiority over using the inhaled corticosteroids and long-acting inhaled beta$_2$-agonists in separate inhalers.

OR

- **Increase the dose of inhaled corticosteroids *and* add a long-acting inhaled beta$_2$-agonist** (SRE-Evidence B). This approach should be reserved for those patients experiencing recurring severe exacerbations requiring oral prednisone, emergency department visits, or hospitalizations. In a 1-year trial of combination therapy, the addition of long-acting inhaled beta$_2$-agonists to either low-dose or high-dose inhaled corticosteroids significantly reduced both mild and severe exacerbations (Pauwels et al. 1997). In addition, fewer exacerbations occurred in the high-dose inhaled corticosteroid group compared with the lower-dose group, although statistical analysis was not done.

OR

- Give inhaled corticosteroids as monotherapy by increasing the dose within the medium-dose range (SRE-Evidence A, B). This approach is another preferred treatment option for young children; it is an alternative, but not preferred, treatment option for older children and adults. Studies of adults in which the dose of inhaled corticosteroids was at least doubled consistently demonstrate improved lung function and other outcomes in those patients not completely controlled on low-to-medium doses of inhaled corticosteroids, but these results are consistently less effective than adding a long-acting inhaled beta$_2$-agonist (SRE-Evidence A, B).

OR

- **Add a leukotriene modifier or theophylline to inhaled corticosteroids** (SRE-Evidence B; Evidence B). The addition of leukotriene modifiers and theophylline has produced modest improvement in lung function and some other outcomes in patients not completely controlled on inhaled corticosteroids. The addition of theophylline, however, has not been shown to be more effective than doubling the dose of inhaled corticosteroids (Evans et al. 1997; Ukena et al. 1997). The leukotriene modifiers have produced improvements in lung function and in some but not all measures of asthma control in patients incompletely controlled on inhaled corticosteroids (Laviolette et al. 1999). In addition, the leukotriene modifiers allow slightly more patients to be taken off inhaled corticosteroids than does placebo (11 percent difference) (Lofdahl et al. 1999). The addition of the leukotriene modifiers to inhaled corticosteroids has not been compared with doubling the dose of inhaled corticosteroids. Direct comparisons of the addition of a leukotriene modifier or a long-acting inhaled beta$_2$-agonist to therapy for patients incompletely controlled on inhaled corticosteroids show significantly greater improvement in lung function and other measures of asthma control for patients receiving the long-acting inhaled beta$_2$-agonist and inhaled corticosteroid combination (Busse et al. 1999; Nelson et al. 2000). Thus, although the combination of inhaled corticosteroids and either theophylline or leukotriene modifier is not the preferred approach, considerations favoring one of these alternative combinations would be the patient's intolerance of the side effects of the long-acting inhaled beta$_2$-agonist, marked preference for oral therapy, and demonstration of superior responsiveness to the alternative class of drug, as well as financial considerations (theophylline is the least expensive).

Specific issues for children. **Recommendations on combination therapy for children younger than 12 years of age with moderate persistent asthma are based on extrapolations from studies in older children and adults and on expert opinion** (Evidence B, D). None of the adjunctive therapy combinations have been adequately studied in children younger than 12 years of age, and they have not been studied at all in children younger than 4 years of age. One negative study of combination therapy in children with mild or moderate persistent asthma failed to establish a need in the study participants at baseline for more therapy than low-dose inhaled corticosteroids and thus did not sufficiently address the question of combination therapy (Verberne et al. 1998). In one study in children 4 to 16 years of age with moderate or severe asthma, the addition of a long-acting beta$_2$-agonist produced a clear benefit compared to placebo (Russell et al. 1995). In a recent crossover comparison of children 6 to 14 years of age on inhaled corticosteroids, no significant difference was found with the addition of the LTRA montelukast in the primary outcome measure FEV$_1$, but a small reduction in as-needed short-acting beta$_2$-agonist use (.33 puffs/day) in favor of LTRA was found. No difference was found for worsening asthma, asthma attacks, or quality of life (Simons et al. 2001). Studies of the addition of theophylline to inhaled corticosteroids in children 6 to 19 years of age showed both a benefit (Nassif et al. 1981) and no benefit (Meltzer et al. 1992). Neither of these theophylline studies is of high enough quality to generate a recommendation. Finally, there is only one study on adjunctive therapy that included children as young as 4 years of age, and there are no studies in children younger than 4 years of age.

Step 4: Severe Persistent Asthma

Patients with severe persistent asthma require high doses of inhaled corticosteroids and a long-acting inhaled beta$_2$-agonist and, if needed, an oral corticosteroid (Evidence B). It is the opinion of the Expert Panel that consultation with an asthma specialist is recommended for patients with severe persistent asthma. Evidence to date does not support using a third long-term-control medication added to inhaled corticosteroids and long-acting inhaled beta$_2$-agonists in order to avoid using systemic corticosteroid therapy (Evidence C). A study found no benefit for the addition of an LTRA to high doses of inhaled corticosteroids and, for most patients in the study, another medication (either theophylline, a long-acting beta$_2$-agonist, oral corticosteroid, or a combination) (Robinson et al. 2001). Similar studies of other long-term-control medications added to the combination of medium-to-high doses of inhaled corticosteroids and long-acting inhaled beta$_2$-agonists in severe persistent asthma are not available.

Patients whose asthma is not controlled on high doses of inhaled corticosteroids and the addition of long-acting inhaled beta$_2$-agonists also will need oral systemic corticosteroids on a regularly scheduled, long-term basis. For patients who require long-term systemic corticosteroids:

- Use the lowest possible dose (single dose daily or, preferably, on alternate days).
- Monitor patients closely for corticosteroid adverse side effects (see component 3—Medications).
- When control of asthma is achieved, make persistent attempts to reduce systemic corticosteroids. High doses of inhaled corticosteroids are preferable to systemic corticosteroids because inhaled corticosteroids have fewer systemic effects.
- Recommend consultation with an asthma specialist.

Recommendations for Future Research

The Panel recommends the following research to clarify treatment options:

- Long-term studies to examine the effect of adjunctive therapy on possible loss in pulmonary function and the natural history of asthma—hospitalization, exacerbations, and decline in pulmonary function.
- Studies of noninvasive markers that would give a composite picture of both disease activity (e.g., inflammation) and disease control. These could be used as surrogate markers for overall asthma control to guide therapy. Ideally, such markers would be more efficient than gauging a patient's response to therapy following a relatively long therapeutic trial.
- Long-term studies to examine the importance of the greater suppression of inflammation achievable with higher doses of inhaled corticosteroids compared with adjunctive therapy. Low doses of inhaled cortico-

steroids usually are sufficient for improvement in lung function and control of asthma symptoms but may not suppress inflammation to the same extent as higher doses. Studies to assess the value of maximum suppression of inflammation vis-a-vis therapeutic control will contribute to understanding the appropriate use of inhaled corticosteroids and adjunctive therapy.

- Evaluations of adjunctive therapies in children younger than 12 years of age.

Key Evidence Tables

TABLE 1–6. Meta-Analysis: Lung Function Outcomes for Studies Comparing the Addition of Long-Acting Beta$_2$-Agonists to a Fixed Dose of Inhaled Corticosteroids

Meta-Analysis	Effect Size Estimate	95% CI	Test for Homogeneity P-Value	Treatment Effect Estimate	95% CI
FEV$_1$: Combined Studies (n = 14)	0.334	0.241, 0.428	0.10	0.17 L 3.71% pred	0.12, 0.22 2.67, 4.75
FEV$_1$: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 3)	0.319	0.139, 0.499	0.14	0.17 L 3.43% pred	0.07, 0.26 1.54, 5.54
FEV$_1$: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (N = 11)	0.368	0.257, 0.478	0.20	0.19 L 4.08% pred	0.13, 0.25 2.85, 5.30
PEF: Combined studies (n = 9)	0.581	0.417, 0.745	0.0034	24.68 L/min 7.26% pred	17.70, 31.65 5.21, 9.31
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 4)	0.643	0.460, 0.826	0.17	27.33 L/min 8.04% pred	19.55, 35.10 5.75, 10.32
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (n = 8)	0.630	0.478, 0.781	0.06	26.77 L/min 7.88% pred	20.32, 33.19 5.98, 9.76

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

TABLE 1–7. Meta-Analysis: Medication Use Outcomes for Studies Comparing the Addition of Long-Acting Beta$_2$-Agonists to a Fixed Dose of Inhaled Corticosteroids

Meta-Analysis	Treatment Effect Estimate	95% CI	Test for Homogeneity P-Value
Puffs/day: Combined studies (n = 6)	-1.18	-1.56, -0.80	0.018
Puffs/day: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 3)	-1.34	-1.87, -0.84	0.20
Puffs/day: Sensitivity analysis by quality: Studies meet all generic quality criteria except allocation concealment (n = 5)	-1.00	-1.34, -0.66	0.14

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

TABLE 1–8. Meta-Analysis: Lung Function Outcomes for Studies Comparing a Lower Dose of Inhaled Corticosteroids Plus Long-Acting Inhaled Beta$_2$-Agonists vs. an Increased Dose of Inhaled Corticosteroids

Meta-Analysis	Effect Size Estimate	95% CI	Test for Homogeneity P-Value	Treatment Effect Estimate	95% CI
FEV$_1$: Combined studies (n = 8)	0.209	0.133, 0.285	0.93	0.11 L 2.32% pred	0.07, 0.15 1.48-3.16
FEV$_1$: Sensitivity analysis by quality: Studies that that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 4)	0.203	0.107, 0.299	0.94	0.11 L 2.25% pred	0.06, 0.16 1.19, 3.32
FEV$_1$: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (n = 7)	0.212	0.134, 0.290	0.88	0.11 L 2.35% pred	0.07, 0.15 1.49, 3.22
PEF: Combined studies (n = 10)	0.310	0.192, 0.429	0.0002	11.6 L/min 3.4% pred	5.2-18.0 1.5-5.3
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 4)	0.300	0.030, 0.569	0.000007	12.75 L/min 3.75% pred	1.28, 24.18 0.38, 7.11
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (n = 7)	0.296	0.143, 0.449	0.00005	12.58 L/min 3.7% pred	6.08, 19.08 1.79, 5.61

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Key Evidence Tables

TABLE 1–9. Study Characteristics

Citation	Study Design	Study Setting
Graham, Milton, Knowles et al. 1982	Randomized, double-blind, placebo-controlled, parallel group trial	Country: United Kingdom Funding: Government grant Tx setting: University Hospital, inpatient setting
Shapiro, Eggleston, Pierson et al. 1974	Randomized, double-blind, placebo-controlled, parallel group trial	Country: United States Funding: Pharm Industry and Government grant Tx setting: Hospital, inpatient setting

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

TABLE 1–10. Study Parameters

Citation	Study Arm	Treatment
Graham, Milton, Knowles et al. 1982	Placebo	Placebo tablet 3 times per day Oral prednisolone (20–60 mg/day) and/or IV hydrocortisone (100–200 mg every 4 to 6 hours) Regularly scheduled beta$_2$-agonists and/or phosphodiesterase inhibitors Chest physiotherapy
	Antibiotics	Amoxicillin 500 mg 3 times per day Oral prednisolone (20–60 mg/day) and/or IV hydrocortisone (100–200 mg every 4 to 6 hours) Regularly scheduled beta$_2$-agonists and/or phosphodiesterase inhibitors Chest physiotherapy
Shapiro, Eggleston, Pierson et al. 1974	Placebo	Placebo 4 times per day for 6 days IV hydrocortisone (7 mg/kg/24 hr) for 24 hr, followed by oral prednisone IV aminophylline (15 mg/kg/24 hr) for 24 hr, followed by oral theophylline Nebulized beta$_2$-agonists q30 min x 4, then as needed
	Antibiotics	Hetacillin 100 mg/kg/24hr for at least 24 hr, followed by oral hetacillin 225 mg 4 times per day for 6 days IV hydrocortisone (7 mg/kg/24 hr) for 24 hr, followed by oral prednisone IV aminophylline (15 mg/kg/24 hr) for 24 hr, followed by oral theophylline Nebulized beta$_2$-agonists q30 min x 4, then as needed

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Asthma Severity	Eligibility
Stated: Not specified Estimated: Unable to estimate	Eligibility assessed on admission to hospital with asthma exacerbation: + FEV_1 of 1.5L or less and/or PEF of 150 l/min + Reversibility of FEV_1 at least 15% spontaneously or after inhalation of $beta_2$-agonist Exclusions: Evidence of pneumonia on CXR, history of penicillin allergy
Stated: Not specified Estimated: Unable to estimate	Eligibility assessed on admission to hospital with asthma exacerbation: + Severe bronchospasm, lack of response to subcutaneous epinephrine Exclusions: Clinical evidence of bacterial infection; recent use of antibiotics

Comments
60 patients enrolled with 71 exacerbations. Unit of analysis by exacerbations.
Culture-proven bacterial source of infection found in two patients on admission and two patients on discharge
37 patients enrolled with 44 exacerbations, unit of analysis by exacerbation

REFERENCES

Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44*. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Busse W, Nelson H, Wolfe J, Kalberg C, Yancey SW, Rickard K. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. *J Allergy Clin Immunol* 1999;103(6):1075–80.

Davies B, Brooks G, Devoy M. The efficacy and safety of salmeterol compared to theophylline: meta-analysis of nine controlled studies. *Respir Med* 1998;92(2):256–63.

Eickelberg O, Roth M, Lorx R, Bruce V, Rudiger J, Johnson M, Block LH. Ligand-independent activation of the glucocorticoid receptor by beta$_2$-adrenergic receptor agonists in primary human lung fibroblasts and vascular smooth muscle cells. *J Biol Chem* 1999 Jan 8;274(2):1005–10.

Evans DJ, Taylor DA, Zetterstrom O, et al. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997 337(20):1412–8.

Fjellbirkeland L, Gulsvik A, Palmer JB. The efficacy and tolerability of inhaled salmeterol and individually dose-titrated, sustained-release theophylline in patients with reversible airways disease. *Respir Med* 1994;88(8):599–607.

Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;344(8917):219–24.

Laviolette M, Malmstrom K, Lu S, Chervinsky P, Pujet JC, Peszek I, Zhang J, Reiss TF. Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. *Am J Respir Crit Care Med* 1999; 160(6):1862–8.

Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske Jr RF, Sorkness CA, Kraft M, Fish JE, Peters SP, Craig T et al. Long-acting β_2-agonist monotherapy vs. continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285(20):2583–93.

Lemanske Jr RF, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, Drazen JM, Chinchilli VM, Craig T, Fish JE, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. *JAMA* 2001;285(20):2594–603.

Lim S, Jatakanon A, Gordon D, Macdonald C, Chung KF, Barnes PJ. Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. *Thorax* 2000;55(10):837–41.

Lofdahl CG, Reiss TF, Leff JA, Israel E, Noonan MJ, Finn AF, Seidenberg BC, Capizzi T, Kundu S, Godard P. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. *BMJ* 1999;319(7202):87–90.

McIvor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. *Am J Respir Crit Care Med* 1998;158(3):924–30.

Meltzer EO, Orgel HA, Ellis EF, Eigen HN, Hemstreet MP. Long-term comparison of three combinations of albuterol, theophylline, and beclomethasone in children with chronic asthma. *J Allergy Clin Immunol* 1992 Jul;90(1):2–11.

Muir JF, Bertin L, Georges D. French Multicentre Study Group. Salmeterol versus slow release theophylline combined with ketotifen in nocturnal asthma: a multicenter study. *Eur Respir J* 1992;5(10):1197–200.

Nassif EG, Weinberger M, Thompson R, Huntley W. The value of maintenance theophylline in steroid-dependent asthma. *N Engl J Med* 1981 Jan 8;304(2):71–5.

Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Richard K, Knobil K. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. *J Allergy Clin Immunol* 2000;106(6):1088–95.

Paggiaro PL, Giannini D, Di Franco A, Testi R. European Study Group. Comparison of inhaled salmeterol and individually dose-titrated slow-release theophylline in patients with reversible airway obstruction. *Eur Respir J* 1996;9(8):1689–95.

Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337(20):1405–11.

Pierson WE, LaForce CF, Bell TD, MacCosbe PE, Sykes RS, Tinkelman D. Long-term, double-blind comparison of controlled-release albuterol versus sustained-release theophylline in adolescents and adults with asthma. *J Allergy Clin Immunol* 1990;85(3):618–26.

Roberts JR, Desai HI, Gillespie CA, Simons FE. Sustained-release terbutaline vs. sustained-release theophylline in young patients with asthma. *Am J Dis Child* 1986;140(7):650–54.

Russell G, Williams, DA, Weller P, Price JF. Salmeterol xinafoate in children on high dose inhaled steroids. *Ann Allergy Asthma Immunol* 1995;75(5):423–8.

Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 2000;320(7246):1368–73.

Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, Laessig W, Schuster A, Perez-Frias et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr* 2001;138(5):694–8.

Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. The AMPUL Study Group. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. *Am J Respir Crit Care Med* 1999;159(4 Pt 1):1043–51.

Ukena D, Harnest U, Sakalauskas R, Magyar P, Vetter N, Steffen H, Leichtl S, Rathgeb F, Keller A, Steinijans VW. Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. *Eur Respir J* 1997 Dec;10(12):2754–60.

Verberne AA, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. The Dutch Asthma Study Group. *Am J Respir Crit Care Med* 1998;158(1):213–9.

Weinstein SF, Pearlman DS, Bronsky EA, Byrne A, Arledge T, Liddle R, Stahl E. Efficacy of salmeterol xinafoate powder in children with chronic persistent asthma. *Ann Allergy Asthma Immunol* 1998;81(1):51–8.

Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996;153(5):1481–8.

USE OF ANTIBIOTICS TO TREAT ASTHMA EXACERBATIONS

Question

Does routinely adding antibiotics to standard care improve the outcomes of treatment for acute exacerbation of asthma? Does the addition of antibiotics to standard care in the following populations improve the outcomes of treatment for an acute exacerbation of asthma: patients without signs and symptoms of bacterial infection; patients with signs and symptoms of a bacterial infection; patients with signs and symptoms of sinusitis?

Summary Answer to the Question

The available evidence (two randomized, controlled clinical trials) suggests no benefit from antibiotic therapy for asthma exacerbations, whether administered routinely or when suspicion of bacterial infection is low (SRE-Evidence B). No studies addressed the question of greatest relevance to contemporary clinical practice: whether the addition of antibiotics to standard care when signs and symptoms suggest the possibility—but do not clearly indicate the presence—of bacterial infection improves the outcomes of treatment for acute asthma exacerbations.

The NAEPP EPR-2 recommendation has not been changed: antibiotics are not recommended for the treatment of acute asthma exacerbations except as needed for comorbid conditions—e.g., for the patients with fever and purulent sputum, evidence of pneumonia, or suspected bacterial sinusitis.

Rationale for the Question

Asthma exacerbations often are associated with clinical signs of infection, such as purulence of expectorated sputum or nasal discharge. Most asthma exacerbations are associated with infection by a respiratory virus, especially rhinovirus (Nicholson et al. 1993; Johnston et al. 1995), but a small percentage of exacerbations are associated with infection by an atypical bacterium, like *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* (Freymuth et al. 1999). It is widely believed that coincident bacterial sinusitis contributes to asthma exacerbations, and some clinicians have postulated that airway obstruction due to mucus plugging—common in asthma—predisposes patients to bacterial infection of nondraining regions of the lungs.

In the absence of clear signs of bacterial infection (e.g., lobar pulmonary infiltrate on chest radiography distinguishing viral from bacterial infections), infection is often difficult to manage. Viral infections commonly resemble bacterial infections in that they also cause neutrophilic inflammation of the upper and lower airways (Teren et al. 1997; Trigg et al. 1996; Fahy et al. 1995). This difficulty, coupled even with the remote possibility that bacterial infection may be associated with an asthma exacerbation, may account for the frequency with which antibiotics are prescribed in addition to inhaled bronchodilators, inhaled or systemic corticosteroids, and supplemental oxygen.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

In addition to the selection criteria for studies related to all topics in the SRE (described in the Introduction section), studies for this question were included in which standard care (asthma medications) plus antibiotics was compared with standard care alone in the treatment of acute asthma exacerbations. Patient populations included patients without signs and symptoms of bacterial infection, patients with signs and symptoms of bacterial infection, and patients with signs and symptoms of sinusitis.

Summary of Findings

Studies

Only two randomized, double-blind, placebo-controlled, parallel-group trials—with a total enrollment of 121 patients—have addressed the question of whether routinely adding antibiotics to standard care improves the outcomes of treatment for acute asthma exacerbations (Shapiro et al. 1974; Graham et al. 1982). (See the key evidence tables in this section.) Both trials studied patients hospitalized for asthma exacerbations. Both used a penicillin derivative whose activity against atypical bacteria was unknown. Shapiro and colleagues examined the effects of hetacillin (an analogue of ampicillin; 100 mg/kg every 24 hours for a minimum of 24 hours, then 225 mg four times per day for 6 days) in 50 children who did not exhibit clinical evidence of bacterial infection. Graham and colleagues examined the effects of amoxicillin (500 mg three times per day) in 60 adults and adolescents who experienced a total of 71 hospital admissions. Whereas the pediatric study explicitly excluded patients with clinical evidence of bacterial infection, the study of adults and adolescents excluded only patients with evidence of pneumonia on chest radiography. Thus, the populations in these studies consisted primarily of patients without signs or symptoms of bacterial illness, including suspected acute sinusitis.

In both trials, all patients received standard care that included high-dose oral or intravenous corticosteroids and regularly scheduled beta$_2$-agonist treatment. In the pediatric study, all patients were also treated with intravenous aminophylline followed by oral theophylline.

The study design and conduct for these two trials did not meet the SRE criteria for higher quality because of deficiencies in allocation concealment, subject withdrawal, and reporting of power calculations.

The outcomes analyzed included change in FEV$_1$, symptom scores, and length of hospital stay.

Results of Studies

Neither study reported an association—or a trend towards an association—between antibiotic treatment and greater improvement in any asthma outcome. Therefore, available evidence suggests no benefit from the use of antibiotic treatment for asthma exacerbations either routinely or when the suspicion of bacterial infection is minimal. (See the key evidence tables 1-11 and 1-12.)

Additional Literature/Information

A related question, for which clinical trials data are unavailable, should ask whether the use of an antibiotic active against *Mycoplasma* and *Chlamydia* would alter outcomes. Some recent studies using polymerase chain reaction (PCR)-based methods for detecting specific genomic sequences have suggested that chronic infection with these organisms may contribute to the severity of chronic asthma (Kraft et al. 1998). These highly sensitive methods have not yet been applied to the analysis of airway tissue or secretions obtained from patients suffering acute exacerbations. Thus, there is a theoretical basis for the concept that a subgroup of patients with asthma exacerbations may benefit from treatment with an antibiotic that is active against these atypical bacteria.

The EPR-2 statement that "the use of antibiotics is generally reserved for patients with fever and purulent sputum (discolored because of polymorphonuclear leukocytes, not eosinophils)" comes under scrutiny because low-grade fever also may accompany viral respiratory infections. Furthermore, a recent study shows that discoloration of sputum by polymorphonuclear

TABLE 1–11. Lung Function Outcomes

Citation	Study Arm	Number Enrolled	Number Evaluable	Study Duration (days) (median/range)
Graham, Milton, Knowles et al. 1982	Placebo	71*	32*	8 (3–16)
	Antibiotics	71*	37*	7 (3–25)
Shapiro, Eggleston, Pierson et al. 1974	Placebo	50*	24*	2.9 (SD 1.4)
	Antibiotics	50*	20*	2.5 (SD 0.8)

*Unit of analysis was admission. Number enrolled represented total admissions in both groups, information not provided by group. Number evaluated represents total number of admissions included in analysis.

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

TABLE 1–12. Symptoms/Utilization Outcomes

Citation	Study Arm	Number Enrolled	Number Evaluable	Study Duration (days) (median/range)
Graham, Milton, Knowles et al. 1982	Placebo	34	32	8 (3–16)
	Antibiotics	37	37	7 (3–25)
Shapiro, Eggleston, Pierson et al. 1974	Placebo	24	24	2.9 (SD 1.4)
	Antibiotics	20	20	2.5 (SD 0.8)

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

leukocytes is observed in viral tracheobronchitis, and the sputum from patients suffering from uncomplicated asthma exacerbations commonly contains high numbers of polymorphonuclear leukocytes (Fahy et al. 1995).

Recommendations for EPR Update

No evidence supports changing the EPR-2 recommendation (SRE-Evidence B). The parenthetical statement on page 116 of EPR-2 [“(discolored because of polymorphonuclear leukocytes, not eosinophils)”] should be removed (Evidence C). The recommendation can otherwise stand and is as follows:

> **Antibiotics are not recommended for the treatment of acute asthma exacerbations except as needed for comorbid conditions. Bacterial, *Chlamydia,* or *Mycoplasma* infections infrequently contribute to exacerbations of asthma and therefore the use of antibiotics is generally reserved for patients with fever and purulent sputum and for patients with evidence of pneumonia. When the presence of bacterial sinusitis is suspected, treat with antibiotics.**

Recommendations for Future Research

No studies addressed the question of greatest relevance to contemporary clinical practice—whether the addition of antibiotics to standard care when signs and symptoms suggest the possibility but do not clearly indicate the presence of bacterial infection improves the outcomes of treatment for acute asthma exacerbations. The two trials reviewed excluded the patients most likely to be treated with antibiotics and those with signs or symptoms suggestive of bacterial infection, including suspected acute sinusitis. Studies of the efficacy of antibiotic treatment in this group are needed.

Several studies are needed to clarify the role of antibiotics in the treatment of asthma exacerbations. Questions for research are as follows:

- What is the efficacy of antibiotic treatment in asthma patients most likely to be treated with antibiotics, such as those with signs suggestive of bacterial infection, including suspected acute sinusitis? The role of sinusitis in acute exacerbations of asthma has not been truly defined.
- What is the role of sinusitis in acute exacerbations of asthma or increased asthma severity?
- What is the efficacy of using an antibiotic active against atypical bacteria, given the possibility that such bacteria commonly contribute to asthma exacerbations?
- What would be the value of studies applying modern sensitive methods of detection of atypical bacteria (e.g., PCR-based methods) to samples of airway tissues or secretions obtained at the time of an asthma exacerbation?
- Do antibiotics such as macrolides have a nonantibiotic action (e.g., anti-inflammatory) that is beneficial in asthma patients?

REFERENCES

Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Fahy JV, Jim KW, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. *J Allergy Clin Immunol* 1995;95(4):843–52.

FEV$_1$ Baseline (mean)	FEV$_1$ Final (mean)	P-Value	PEF baseline (mean/range)	PEF final (mean/range)	P-Value
20.9 (<7.3–63)	65.6 (31.5–108.5)		23.8 (<9.4–83.9)	72.8 (32.8–108.1)	
23.1 (<7.3–45.5)	52.3 (10–92.9)	0.039	23.8 (<9.4–47.3)	59 (16.7–95)	0.052
26.5 (SD 15)	49 (SD 17)		NR	NR	
28.3 (SD 11)	61 (SD 19)	NR	NR	NR	

Baseline Symptom Score (median/range)	Final Symptom Score (median/range)	P-Value	Hospital Length of Stay	P-Value
11 (6–12)	4 (4–8)		8 (3–16)	
11 (5–12)	5 (4–9)	NS	7 (3–25)	NS
7.1 (mean) (SD 2.2)	2.5 (SD 2.0)		2.9 (SD 1.4)	
7.1 (mean) (SD 1.8)	2.0 (SD 2.0)	NR	2.5 (SD 0.8)	

Freymuth F, Vabret A, Brouard J, Toutain F, Verdon R, Petijean J, Gouarin S, Duhamel JF, Guillois B. Detection of viral, Chlamydia pneumoniae and Mycoplasma pneumoniae infections in exacerbations of asthma in children. *J Clin Virol* 1999;13(3):131–9.

Graham VA, Milton AF, Knowles GK, Davies RJ. Routine antibiotics in hospital management of acute asthma. *Lancet* 1982;1(8269):418–420.

Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O'Toole S, Myint SH, Tyrell DA, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ* 1995;310(6989):1225–9.

Kraft M, Cassell GH, Henson JE, Watson H, Williamson J, Marmion BP, Gaydos CA, Martin RJ. Detection of Mycoplasma pneumoniae in the airways of adults with chronic asthma. *Am J Respir Crit Care Med* 1998;58(3):998–1001.

Labro MT. Anti-inflammatory activity of macrolides: a new therapeutic potential? *J Antimicrob Chemother* 1998;41(Suppl B):37–46.

Nicholson K, Kent J, Ireland D. Respiratory viruses and exacerbations of asthma in adults. *Br Med J* 1993;307:982–6.

Shapiro GG, Eggleston PA, Pierson WE, Ray CG, Bierman CW. Double-blind study of the effectiveness of a broad spectrum antibiotic in status asthmaticus. *Pediatrics* 1974;53(6):867–72.

Teran LM, Johnston SL, Schroder JM, Church MK, Holgate ST. Role of nasal interleukin-8 in neutrophil recruitment and activation in children with virus-induced asthma. *Am J Respir Crit Care Med* 1997;155(4):1362–6.

Trigg CJ, Nicholson KG, Wang JH, Ireland DC, Jordan S, Duddle JM, Hamilton S, Davies RJ. Bronchial inflammation and the common cold: a comparison of atopic and non-atopic individuals. *Clin Exp Allergy* 1996;26(6):665–76.